The Role of Health Behaviours in Colorectal Cancer Risk and Screening Uptake

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Abstract

Background

The burden of colorectal cancer is high in developed countries and is now increasing in developing countries. Socioeconomic disparities in colorectal cancer incidence and screening uptake are global issues. Identifying the mediator of the association between socioeconomic status and colorectal cancer will guide appropriate public health interventions to reduce the burden of colorectal cancer. The aims of this thesis were to estimate the associations between socioeconomic status and colorectal cancer outcomes and identify mediators of the associations.

Methods

To demonstrate the current stage of knowledge, systematic reviews and meta-analyses were conducted to estimate the association between socioeconomic status (educational attainment, income and composite socioeconomic status indicators based on area of residence) and colorectal cancer outcomes (screening uptake and risk). Subgroup analyses and sensitivity analyses of the meta-regression were conducted to assess the covariates' effect on the pooled result estimates and the heterogeneity.

To identify the mediators of the association between socioeconomic status (educational attainment and Index of Relative Socioeconomic Disadvantage (IRSD)) and colorectal cancer outcomes (screening uptake and risk), mediation analysis (*medeff* and *paramed* commands) based on the counterfactual framework was performed. The possible mediators were health behaviours (obesity and smoking) and colorectal cancer screening

uptake (for risk of colorectal cancer). The Australasian Colon Cancer Family Registry was used in the analyses.

Results

For colorectal cancer screening, people in the higher socioeconomic status groups were more likely to participate in colorectal cancer screening than those in the lowest socioeconomic status groups. The meta-analyses showed moderate to high heterogeneity between studies, which was partially explained by the country in which the study was conducted. For risk of colorectal cancer, the risk of rectal cancer was higher for people in the lowest socioeconomic status groups compared to those in the highest socioeconomic status groups. Heterogeneity between studies was partially explained by continent of study and study design.

For colorectal cancer screening, the mediation analysis showed that 13.7% of the association between educational attainment and colorectal cancer screening uptake and 15.5% of the association between IRSD and screening uptake were mediated via smoking. For risk of colorectal cancer, the mediation analysis showed no evidence of the mediated effects of health behaviours and colorectal cancer screening uptake on the association between socioeconomic status and risk of colorectal cancer.

Conclusion

Socioeconomic disparities in colorectal cancer are persisting globally and in Australia. I found evidence of the mediated effect of health behaviours on the association between socioeconomic status and colorectal cancer screening uptake. Advances in mediation

analysis such as multiple mediator models and simulation studies will enable more comprehensive analyses of the socioeconomic disparities in colorectal cancer.

Declaration

This is to certify that

The thesis comprises only my original work towards the PhD except where indicated in the Preface,

Due acknowledgement has been made in the text to all other material used,

The thesis is 28,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Kanlaya Jongcherdchootrakul

December 2019

Preface

During these four years, the author received fully financial support from Ministry of Science and Technology of the Royal Thai Government. Moreover, the author was a recipient of a studentship from Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne between February 2016 and December 2019.

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The publication statuses of four results chapters (Chapter 3–6) are in process of preparation. They are unpublished material.

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Abbreviations

ACCFR The Australasian Colon Cancer Family Registry

CI confidence interval

CRC colorectal cancer

CPS the Census Bureau's Current Population Survey

FIT Faecal Immunochemical Test

FOBT Faecal Occult Blood Test

g gram

gFOBT guaiac-based Faecal Occult Blood Test

GLOBE Health and Living Conditions of the Populations of the Population of Eindhoven and Surroundings (in Dutch)

Hb haemoglobin

HR hazard ratio

IRSD Index of Relative Socioeconomic Disadvantage

μg microgram

NBCSP National Bowel Cancer Screening Program

NDE natural direct effect

NIE	natural indirect effect
NIH–AARP	The National Institutes of Health-American Association of Retired Persons
OR	odds ratio
ROBINS-I	Risk Of Bias In Non-randomizes Studies of Interventions
RR	relative risk
SEIFA	Census of Population and Housing: Socio-Economic Indexes for Areas
SEP	socioeconomic position
SEER	The Surveillance, Epidemiology, and End Results Program
SES	socioeconomic status
SEP	socioeconomic position
SD	standard deviation
US	the United States
USPSTF	the United States Preventive Services Task Force

Chapter 1. Background

1.1. Definition of colorectal cancer

Colorectal (bowel) cancer is a malignancy within the wall of the large intestine, which include the cecum, ascending colon, transverse colon, descending colon, sigmoid and rectum[1]. Symptoms of colorectal cancer are not specific and can include anaemia and changes in usual bowel habit. In general, the symptoms become evident when the cancer is in an advanced stage. Colorectal cancer gradually progresses from a precancerous lesion to malignancy over several years. The hypothesis of the adenoma–carcinoma sequence of colorectal cancer is supported by several observational studies of hereditary polyposis syndrome[2, 3] and the efficacy of polypectomy on colorectal cancer incidence and mortality[4-9].

While adenomas can become malignant, most do not. The likelihood of a polyp becoming cancer depends on its size, histology, tumour location, number of lesions and the patient's age[10-12]. Generally, larger adenomas, those with greater dysplasia[12], and sessile (flat) serrated adenomas[10] are more likely to become malignant.

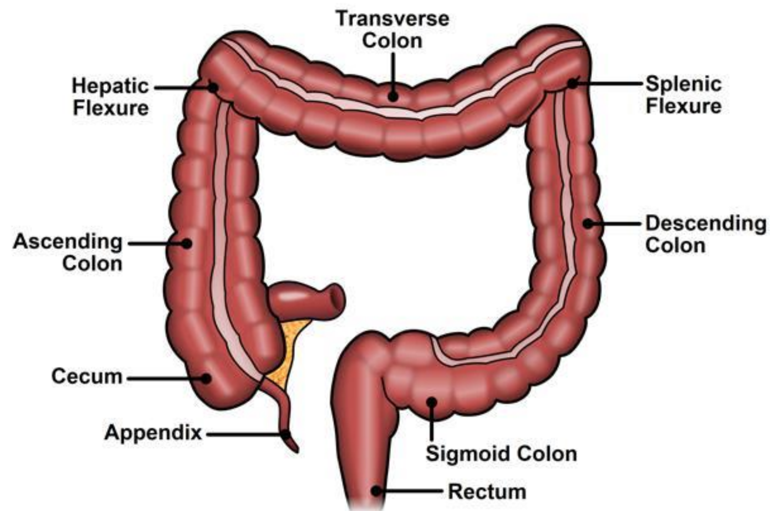


Figure 1.1 Anatomy of the colon[13]

The location of a colorectal cancer tumour is one of the predictors of prognosis and mortality. The proximal section of the large bowel is usually defined as being proximal to the splenic flexure that includes the cecum, ascending colon and transverse colon (Figure 1.1)[1]. The distal to splenic flexure, which includes the descending colon, sigmoid colon and rectum, is defined as the distal section (Figure 1.1). Advanced colorectal cancers are more likely to be found in the proximal section of the large bowel than in the distal section[14]. Adenomas are more commonly found in the distal section than in the proximal section of the large bowel[9, 15-18], but invasive adenocarcinoma is more common in the rectum than in the colon[19]. The natural history of colorectal cancer, in terms of its gradual progression, precancerous lesions and tumour location, suggests that colorectal cancer can be prevented by adenoma or polyp removal. Therefore, mortality from colorectal cancer will be decreased by screening and early detection of adenomas (Figure 1.2).

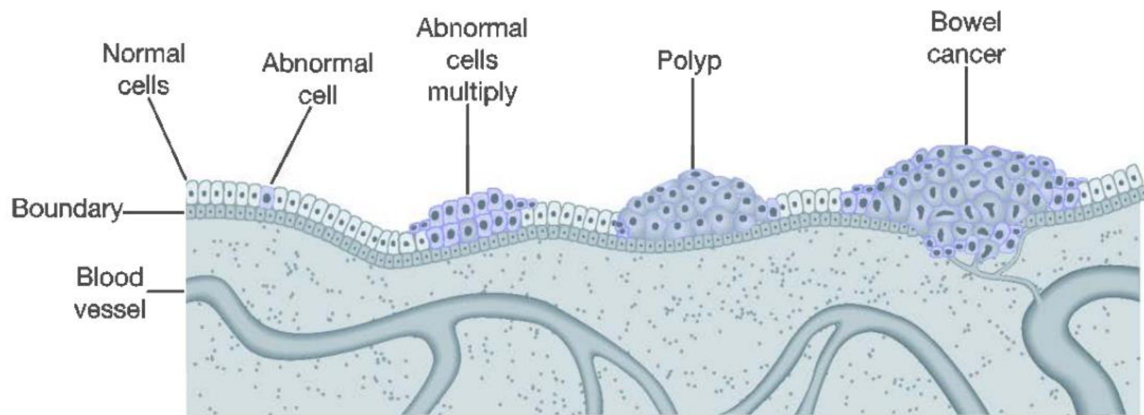


Figure 1.2 Beginnings of bowel cancer[20]

1.2. Colorectal cancer screening

Widely used colorectal cancer screening modalities include stool-based tests (guaiac-based faecal occult blood test [gFOBT] and faecal immunochemical test [FIT]), endoscopy (flexible sigmoidoscopy and colonoscopy), and imaging (double-contrast barium enema and magnetic resonance colonography). Of these, only gFOBT[21-25] and screening sigmoidoscopy[26-29] are supported by evidence of decreased colorectal cancer mortality from randomised controlled trials. Meta-analyses of the effectiveness of colorectal cancer screening programs showed a 15–22% decrease in colorectal cancer in people who screened with gFOBT compared with those without screening[1, 30, 31]. Similarly, colorectal cancer mortality declined by 26–27% in people who screened with flexible sigmoidoscopy compared with those without screening[1, 30].

Non-invasive stool-based screening tests (gFOBT and FIT) are used in national bowel cancer screening programs in several countries such as the United Kingdom, France and Australia. The gFOBT detects peroxidase of haem and is more sensitive to bleeding from the colon and rectum but rarely detects haem from the diet or upper gastrointestinal tract.

There have been three large randomised controlled trials of the effectiveness of gFOBT for reducing colorectal cancer mortality: the Minnesota trial[25] (30 years of follow-up; annual screening relative risk [RR] 0.68 and 95% confidence interval [CI] 0.56, 0.82; biennial screening RR 0.78 and 95% CI 0.65, 0.93); the Nottingham trial[24] (19.5 years of follow-up; biennial screening RR 0.88 and 95% CI 0.79, 0.98); and the Danish trial[22] (17 years of follow-up; biennial screening RR 0.84 and 95% CI 0.73, 0.96). These studies reported that colorectal cancer mortality decreased by 12–32% in people screened with gFOBT compared with control groups[22, 24, 25]. Two other population-based randomised controlled trials that were conducted in France[21] (11 years of follow-up; biennial screening RR 0.84 and 95% CI 0.71, 0.99) and Sweden[23] (19 years of follow-up; biennial screening RR 0.84 and 95% CI 0.71, 0.99) also showed evidence of decreased colorectal cancer mortality by using biennial gFOBT screening.

The gFOBT has low sensitivity and high false positive rates due to the peroxidase process[32, 33]. In contrast, the FIT detects human hemoglobulin by immune assay and is therefore more sensitive than the gFOBT[34-37]. Therefore, FIT has become the adopted colorectal cancer screening for average-risk adults worldwide[38-40]. However, there are several issues of FIT test which are ongoing debate, such as, the number of faeces samples to be tested[41, 42] and the best cut-off for positivity[41, 43]. The cut-off level of haemoglobin (Hb) per gram (g) faeces affects positive predictive value, sensitivity and specificity of the test. Moreover, the practical cut-off level should be related to ability of diagnosis by using colonoscopy. Studies in the Netherlands are using a cut-off of 10 microgram (µg) Hb/g faeces[42]. Similarly, the cut-off of 9 µg Hb/g faeces is suggested in Germany[44]. While the cut-off of 20 µg Hb/g faeces is commonly used in the United States[43].

Endoscopy (including flexible sigmoidoscopy and colonoscopy) is a method of screening for colorectal cancer that can visualise and remove polyps or adenomas, thereby screening for and preventing colorectal cancer at the same time. The effectiveness of flexible sigmoidoscopy in decreasing colorectal cancer mortality has been shown in three randomised controlled trials (based on intention to treat analysis) that were conducted in Norway[27] (11.2 years of follow-up; RR 0.73 and 95% CI 0.56, 0.94), the United States[28] (12.1 years of follow-up; RR 0.74, and 95% CI 0.63, 0.87) and the United Kingdom[26] (17.0 years of follow-up; RR 0.70 and 95% CI 0.62, 0.79). An Italian study[29] that used per protocol analysis reported a 38% (95% CI 4%, 60%) decline in colorectal cancer mortality in those who had flexible sigmoidoscopy compared with those without any screening.

These four randomised controlled trials also demonstrated the effectiveness of flexible sigmoidoscopy in reducing colorectal cancer incidence (Norway study[27] RR 0.80, 95% CI 0.70, 0.92; United States study[28] RR 0.79, 95% CI 0.72, 0.85; Italian study[29] RR 0.82, 95% CI 0.69, 0.96; and United Kingdom study[26] HR 0.74, 95% CI 0.70, 0.80). Cancer detection by flexible sigmoidoscopy and cancer incidence reduction was greater in the distal colon and rectum than in the proximal colon[26-29].

Colonoscopy can explore the entire colon and rectum, while flexible sigmoidoscopy only examines the bowel up to the sigmoid colon. To date, there has been no randomised controlled trial of the effectiveness of colonoscopy in reducing colorectal cancer mortality and incidence. Analysis of 22 years of follow-up[45] from the Nurses' Health Study and the Health Professionals Follow-up Study found a 68% (95% CI 55%, 76%) decrease in colorectal cancer mortality in those who had screening colonoscopy compared with those

without any screening. The screening colonoscopy also reduced mortality from proximal colorectal cancer by 53% (95% CI 24%, 71%)[(45)]. Therefore, colonoscopy is now considered the standard method of colorectal cancer screening by the US Preventive Services Task Force[(46)].

In Australia, the National Bowel Cancer Screening Program was started in 2006[(20)]. This program aims to reduce the morbidity and mortality of colorectal cancer. Australian Government sends free of charge biennial FIT home test kits, which consist of: the FIT test; instruction of how to collect the sample; and information about bowel cancer, to eligible Australians aged 50–74 years via mail. The tests are returned by participants for testing by pathology laboratories. People can also ask their general practitioners about bowel cancer screening and request the test if they are eligible. Additionally, information about the National Bowel Cancer Screening Program is available in several languages such as Chinese and Hindi. Participants with a positive screening result (based on detection of blood in their stool sample) are referred to their general practitioners for further investigation. The most participation rate of the National Bowel Cancer Screening Program was 41% in 2015–2016. Of those who participated in 2016, 8.1% had a positive screening result and 68% of these continued to a diagnosis assessment[(20)]. In 2016, 1 in 26 participants were diagnosed with a confirmed or suspected colorectal cancer and 1 in 9 participants were diagnosed with adenomas[(20)]. The Australian Institute of Health and Welfare stated that the National Bowel Cancer Screening Program is reaching its objective because the risk of death from colorectal cancer was increased by 68% (hazard ratio [HR] 1.68, 95% CI 1.48, 1.92) in non-participants of the National Bowel Cancer Screening Program compared with the participants[(47)]. After correction for the potential lead-time in screen-detected cancers, the risk of death from colorectal cancer was

increased by 15% (HR 1.15, 95% CI 1.01, 1.31) in the non-participants compared with the participants[47]. However, the screening by FIT and diagnosis by endoscopy among Australians were low that should be improved in order to prevent the further colorectal cancer cases and deaths.

1.3. Current colorectal cancer incidence and mortality

Colorectal cancer is one of the diseases currently identified as an indicator of demographic and epidemiological transition[48, 49]. The burden of colorectal cancer is high in developed countries and is now increasing in developing countries. GLOBOCAN (a cancer statistics database from the International Agency for Research on Cancer) estimated that there were 1.8 million new colorectal cancer cases and 881,000 deaths from colorectal cancer worldwide in 2018[50]. Colorectal cancer has been in the top three most commonly diagnosed cancers for men and women since 2008[50-52]. The highest age-standardised incidences of colon cancer were found in Europe, Australia/New Zealand, North America and eastern Asia (Republic of Korea and Japan) (Figure 1.3a)[50]. In contrast, the age-standardised incidences of colon cancer were lowest in Africa and southern Asia. Similar distributions were found for rectal cancer (Figure 1.3b).

Colorectal cancer is the fourth most common cancer death among men since 2002[50-53] and the third[51, 52] or fourth[50] most common cancer death among women. Deaths by colon and rectum cancers increased by 23.2% (95% CI 20.6%, 26.0%) from 2005 to 2015 with an age-standardised mortality rate (per 100,000) of 14.0 (95% CI 13.8, 14.2) in 2005 and 13.0 (95% CI 12.7, 13.4) in 2015[54]. Colorectal cancer is the 27th highest cause of global years of life lost due to premature mortality in 2015, increasing from the 40th highest in 1990 and 28th highest in 2005[54].

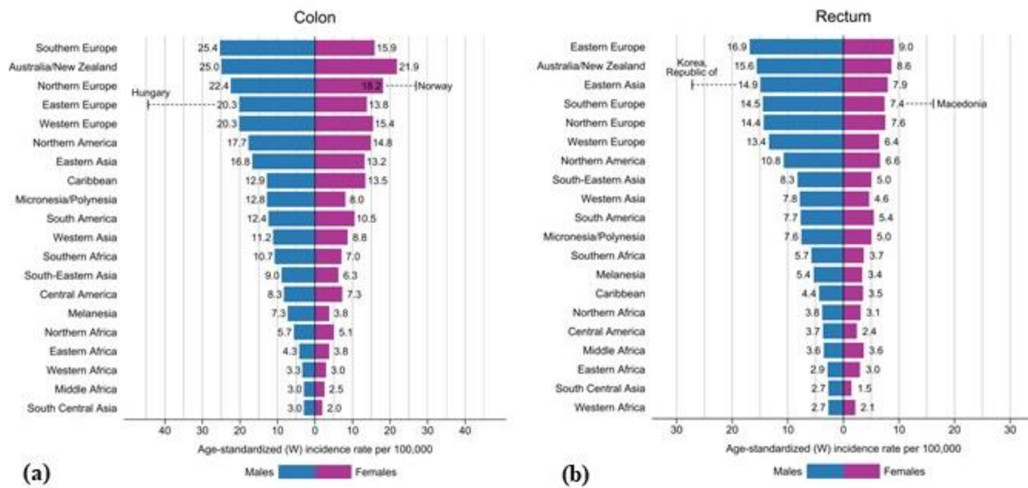


Figure 1.3 Region-specific age-standardised incidence by sex for cancers of the (a) colon and (b) rectum in 2018[50]

Since 2002, Australia and New Zealand have had the world's highest age-standardised incidences of colorectal cancer[50-53]. In 2018, colorectal cancer was the third most commonly diagnosed cancer in Australia and the second leading cause of cancer deaths[55]. The estimated numbers of new colorectal cancer cases and deaths in Australia were 17,004 and 4,129 respectively, an average of 47 new cases and 11 deaths per day[55]. Age-standardised incidence rates for colorectal cancer (in 1982–2018) varied between 58 and 66 cases per 100,000 persons[55]. The age-specific incidence for people aged 20–39 years is increasing, whereas the age-specific incidence for people aged 40 years and older is stable[56]. The age-standardised mortality rate (per 100,000 population) for colorectal cancer has declined from 31.5 in 1982 to 13.5 in 2018[55]. The overall 5-year relative survival rate for colorectal cancer was 69.5% in 2011–2016. An earlier stage of diagnosis has a higher 5-year survival rate; nearly all (98.6%) stage I colorectal cancer cases survived for 5 years while only 13.4% of the stage IV colorectal cancer cases survived

for 5 years[55]. Australians lost more than 90,000 disability-adjusted life years due to colorectal cancer in 2011; this was 11% of the total cancer burden[55]. Colorectal cancer was ranked as the second highest cause of cancer burden[55].

In Australia, men are 1.4 times more likely to be diagnosed with, and 1.3 times more likely to die from, colorectal cancer compared with women[55]. There is a greater risk of developing colorectal cancer with advancing age[55]. The most common site of colorectal cancer was the rectum (25.7% of colorectal cancer diagnosed) followed by the sigmoid colon (18.5%), caecum (13.1%), and ascending colon (12.1%). Adenocarcinoma (90.4%) was the most common histology group in 2013[55]. In 2011, 17.7% of diagnosed colorectal cancer was stage IV, with around 23% in each of stages I, II, and III.

1.4. Risk factors for colorectal cancer

Lifestyle and environmental factors affect both colorectal cancer burden and participation in appropriate colorectal cancer screening. In Australia, 18% of colorectal cancer cases were attributable to red and processed meat consumption[57], while physical inactivity, overweight and obesity, and alcohol use were responsible for 16.2%[58], 12.8%[59] and 5.4%[60] of the colorectal cancer burden, respectively. Moreover, bowel cancer awareness, which is reducing the risky behaviours and doing the screening frequently, has played an essential role on colorectal cancer's preventions and controls.

Most colorectal cancer cases are not due to inherited high-risk genetic mutations. Only 5–7% of colorectal cancers are due to hereditary colorectal cancer syndromes such as Lynch syndrome (hereditary nonpolyposis colorectal cancer), and familial adenomatous polyposis[61, 62]. A family history of colorectal cancer in first-degree relatives increases

the risk of developing colorectal cancer[63]. Increasing age, being male, and being Ashkenazi Jewish[64] or black[65] increase the risk of colorectal cancer. These risk factors are non-modifiable and intensive surveillance for colorectal cancer in these groups will be the most effective intervention to reduce the effect of these risk factors.

Modified lifestyle and environmental factors account for most cases of colorectal cancer. The World Cancer Research Fund and the American Institute for Cancer Research[66] reported that there is strong evidence that the consumption of wholegrains, dietary fibre, dairy products and calcium supplements decreases the risk of colorectal cancer. Being physically active reduces the risk of colon cancer. In contrast, consuming red or processed meat, drinking two or more alcoholic drinks per day, being overweight or obese, or being tall all may increase the risk of colorectal cancer[66]. There is evidence that medications such as aspirin and non-steroidal anti-inflammatory drugs[67, 68], hormone replacement therapy[69] and cyclooxygenase-2 inhibitors[70] reduce the risk of colorectal cancer. However, these medications are not recommended for general use to prevent colorectal cancer because of their side effects, such as cardiovascular disease and gynaecological cancer (particularly from hormone replacement therapy).

Socioeconomic status is another very important risk factor for colorectal cancer. This is seen in the geographical difference in the association between socioeconomic status and risk of colorectal cancer[71, 72]. In a recent systematic review, people with lower socioeconomic status in the United States and Canada had a greater risk of developing colorectal cancer compared with those who had higher socioeconomic status[72]. This is in contrast to Europe, where the risk of colorectal cancer was higher among people with higher socioeconomic status than in people who had lower socioeconomic status. The

reasons for this heterogeneity in association may include differences in lifestyle risk factors and colorectal cancer screening modality between the two continents[71, 72].

1.5. Socioeconomic status indicators

Socioeconomic disparities in health are being investigated for their contribution to cancer risk. People with lower socioeconomic status generally have greater incidence, lower survival and higher mortality rates from cancers compared with people with higher socioeconomic status. Socioeconomic status can be measured in several ways and there is no single best indicator for all studies. Each socioeconomic status indicator – such as educational achievement, income or occupation – has advantages and limitations. In practice, we try to use the indicator that most directly answers our research question and then discuss its advantages and limitations[73]. Education, income and occupation are the traditional indicators of socioeconomic status in epidemiological studies[74] but more recently, area-level measures of socioeconomic status have been used as proxies for traditional measures of socioeconomic status.

Educational achievement is a frequently used indicator of socioeconomic status in health research[74, 75]. In theory, education transfers parents' socioeconomic status to an individual's adulthood socioeconomic status and determines the individual's future occupation and income[74, 75]. The advantages of using education as an indicator of socioeconomic status are that it is relatively easy to measure, has a high response rate, and is available for participants aged 25 years and older. However, education has limitations due to its cohort effect and reverse causality. A cohort effect most likely occurs when there is a wide range of age groups included in a study. Older cohorts are always over-represented in the less educated group, resulting in biased results[75]. Reverse

causality can be shown by the case of illness in childhood that limits school attendance and thereby affects overall education achievement[74].

Income is another commonly used socioeconomic status indicator. It directly measures material resources in a dynamic and short-term context. Income affects health status by increasing access to: health-promoting environments (work and residential), health-enhancing commodities (food and exercise), and health services[74]. Income can be a sensitive question that may cause low response rates or inaccurate answer. Reverse causality can be an issue because poor health likely limits one's ability to work, resulting in an overall lower income. Wealth and poverty level are the standard socioeconomic status indicators related to income. Wealth shows the accumulation of financial and physical assets and is the best indicator for late adults or retirement groups[74]. Poverty level is a relative measure of income and the standard cost of living[73].

Occupation-based measures reflect a person's place in society related to their social standing, income and educational achievements[75]. Occupation is associated with social standing, which is correlated with privileges such as access to better healthcare that may increase the chances for a healthier life[75]. The advantage of using occupation in burden of disease studies is the availability of the information in several data sources such as census or death certification. However, there are limitations to using occupation-based measures of socioeconomic status. First, unhealthy people cannot do some jobs, which is another example of reverse causality. Second, the unemployed, homemakers, retirees and students cannot be categorised using an occupation-based measure. Previous occupation and spouse or parents' occupations are used as a proxy in these cases.

Composite socioeconomic status indicators based on area of residence use aggregated data from individual level and small area to represent the socioeconomic status[76]. Examples of these indicators are the Townsend deprivation index, Carstairs deprivation index and Jarman underprivileged area scores. The composite socioeconomic status indicators based on area of residence are useful for evaluating health policy and health services[74]. Under the assumption that where a person lives can affect their health, an composite socioeconomic status indicator based on area of residence is likely to be a good proxy for individual socioeconomic status[77]. However, the composite indicator always underestimates the true individual effect by misclassification; the larger the area is used, the greater this bias will be[76].

An individual's socioeconomic position is somewhat pre-determined and highly resistant to change. In general, people with advanced skills and higher education are likely to have well-paid and secure jobs. Because education is key to higher socioeconomic status, individuals can ameliorate their socioeconomic position by increasing their education[78]. For example, compulsory education is a good example of public policy that may improve the socioeconomic status of people in deprived groups[78]. Compulsory education may increase literacy rates and create access to better jobs, and in turn, this reduces the health gap between lower and higher socioeconomic status groups.

1.6. Why is socioeconomic status so important in colorectal cancer?

Socioeconomic disparity is one of the most challenging obstacles in public health, especially in cancer prevention and control. For colorectal cancer, lower socioeconomic

status groups generally have higher incidence, lower survival and greater mortality rates of colorectal cancer compared with higher socioeconomic status groups. Additionally, socioeconomic status is associated with several lifestyle behaviours that are risk factors for cancer. People with lower socioeconomic status are more likely to smoke, misuse alcohol, or have a sedentary lifestyle. The causal pathway from socioeconomic status to colorectal cancer risk via these lifestyle behaviours has been identified in American studies[79, 80]. Therefore, health policies or interventions that focus on socioeconomic status and lifestyle factors will directly and indirectly improve the burden of chronic diseases and colorectal cancer.

Identification of under-served or deprived population sub-groups is another means to decrease the health gap between lower and higher socioeconomic groups. Health interventions can be targeted to deprived groups. In the case of colorectal cancer, screening is the most effective intervention to decrease the burden of the disease. Introducing the screening program to deprived population groups will increase their access to healthcare and will reduce the overall burden of colorectal cancer over time. This concept was used to establish guidelines for colorectal cancer screening in the United States and for national bowel cancer screening programs in several European countries; these have helped narrow the health gap by increasing accessibility to screening for deprived groups.

1.7. Social Determinants of Health as a model for examining the role of socioeconomic status in colorectal cancer burden

The Social Determinants of Health framework designed by the World Health Organization's Commission on Social Determinants of Health was updated by Solar and Irwin in 2010 (Figure 1.4)[81]. The framework aims to demonstrate the complexity of social determinates of health by highlighting the different levels of causation, variety of mechanisms from social hierarchies and heterogeneity of conditions of daily life. This comprehensive action-oriented framework guides health policy makers about where and to what degree interventions to reduce health inequities should be enacted. Socioeconomic and political contexts such as governance, social policies, and public policies are analysed for their effect on people's socioeconomic position, which is classified by income, education, and occupational strata. The structural determinants and socioeconomic position are proxies for the socioeconomic and political contexts. Socioeconomic position is related to intermediate determinants of health, which can be material circumstances, behaviours, biological factors, psychosocial factors and the health system. All these components influence exposure in different ways that are associated with an individual's illness or health condition. Illness can also feedback to socioeconomic position and political context. Thus, the Social Determinants of Health Framework is essential for investigating the mechanism by which socioeconomic status affects health outcome via several intermediate factors.

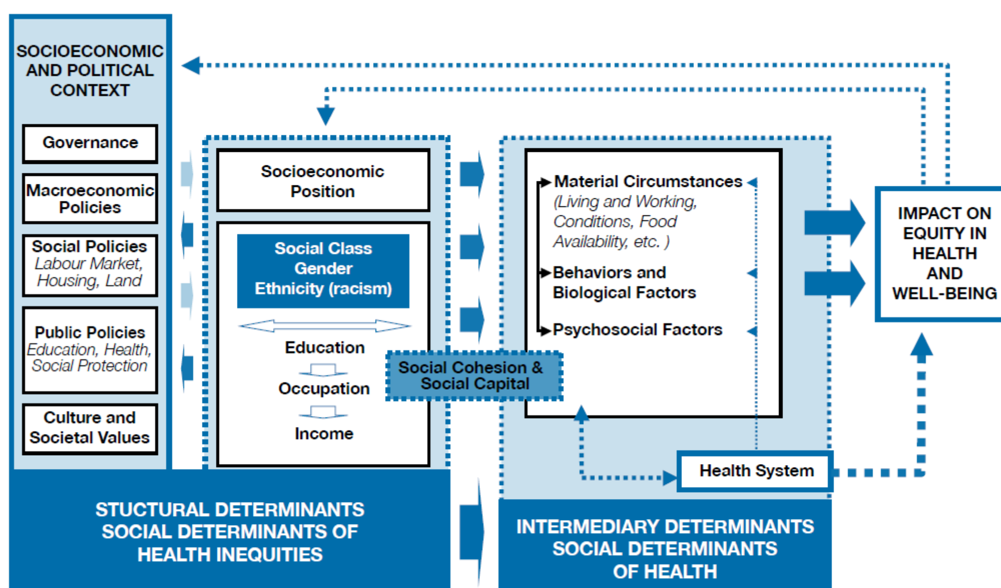


Figure 1.4 The Social Determinants of Health conceptual framework[81]

1.8. Causal inference in studies of socioeconomic disparities

Social epidemiology focuses on the social determinants of health[82] and aims to explore social allocation mechanisms that are likely related to health disparities[83]. Social epidemiology uses surveillance and aetiologic inference studies to investigate the associations between social, economic or cultural factors and health outcomes[82-84]. Surveillance studies measure disease occurrence in different social classes. In studies of aetiologic inference, the causal relationships between socioeconomic status and health outcome are analysed to generate specific, effective and comprehensive interventions on public health[84].

Causality is one of the fundamental issues of social epidemiology[83] because studies of socioeconomic disparities on health depend on observational studies in which socioeconomic status cannot be randomised to participants by the researchers[83]. The

association between socioeconomic status and health that is observed in some studies might not be causal but instead might be due to reverse causation or confounding[78]. Causal effects must be defined in terms of a counterfactual framework to be relevant in these studies[78]. Therefore, due to the complexity of the relationship between social determinants and health outcomes, a comprehensive framework is required that incorporates all covariates and considers nonlinearities and interactions[78].

1.9. Why I am exploring the role of socioeconomic status in both colorectal cancer screening and colorectal cancer risk.

Socioeconomic disparities in colorectal cancer risk continue to reflect differences between North America and Europe that might be caused by different cultural or social characteristics, such as the proportion of risky lifestyle factors and the features of the national colorectal cancer screening program. Colorectal cancer screening uptake does reduce colorectal cancer mortality but access to cancer screening programs continues to be problematic for socioeconomically deprived people. The complex association between socioeconomic status and colorectal cancer risk and screening uptake must be made explicit to inform alternative interventions to address the disparities in burden of disease. Increasing screening uptake and declining colorectal cancer risk among deprived groups are essential to reduce the overall burden of disease and narrow health disparities in colorectal cancer.

1.10. Research gaps, hypothesis and objectives of the thesis

Socioeconomic disparities in colorectal cancer incidence and screening uptake are global issues. Policy makers try to decrease socioeconomic health differences to improve

population health. Comprehensive interventions, which enhance the population's health literacy on prevention and accessibility to standard healthcare, are sustainable ways to decrease this health gap. Identifying and adjusting the mediator of the association between socioeconomic status and colorectal cancer will guide appropriate public health interventions to reduce the burden of colorectal cancer. This thesis aims to understand the socioeconomic disparities on colorectal cancer.

For colorectal cancer screening, my research will provide a comprehensive overview of the published literature on colorectal cancer screening and socioeconomic status and quantify the magnitude of the association between screening participation and socioeconomic status indicators for the different screening modalities. This will update and fill the gap from previous reviews. I will explore the mediated effect of lifestyle factors on the association between socioeconomic status and colorectal cancer screening uptake in Australia using the counterfactual approach. If the effect of socioeconomic status on screening uptake is mediated through these lifestyle factors, interventions to reduce these factors can be justified as a health measure to reduce the socioeconomic disparities in colorectal cancer screening uptake, and thus reduce morbidity and mortality from colorectal cancer.

For colorectal cancer incidence, my research will provide a systematic review and meta-analysis that investigates the association between socioeconomic status and risk of colorectal cancer and explores the possible reasons of the heterogeneity of the association. This may explain the reported[71, 72] geographical difference between North America and Europe. I will also explore the indirect effect of lifestyle factors and colorectal cancer screening uptake on the association between socioeconomic status and colorectal cancer

risk in Australia using the counterfactual approach. If the effect of socioeconomic status on colorectal cancer risk is mediated through the screening uptake or lifestyle factors, interventions to improve lifestyle factors and the screening uptake could also prevent morbidity and mortality from colorectal cancer.

Chapter 2. Methodology

2.1. Introduction

My research explored the relationship between socioeconomic status disparities and colorectal cancer with regards to two main outcomes assessed separately: colorectal cancer screening uptake and colorectal cancer risk. I began by conducting two systematic reviews to evaluate the current state of knowledge of the associations between socioeconomic status and both outcomes. Chapter 3 presents the results of the first systematic review, which evaluates the association between socioeconomic status and colorectal cancer screening. Meta-analyses of the included studies were performed for several screening procedures to estimate the magnitude of the association. Chapter 4 presents the results of the second systematic review and meta-analyses of the included studies to explore the association between socioeconomic status and colorectal cancer risk. Chapter 5 includes a mediation analysis of the effects of health behaviours on the association between socioeconomic status and colorectal cancer screening. Chapter 6 investigates potential mediators of the association between socioeconomic status and colorectal cancer risk. This chapter describes the main methodologies used for each of these chapters.

2.2. The current state of knowledge: systematic review and meta-analysis

Embase, MEDLINE, PsycINFO and the Cochrance library databases were searched to identify relevant studies for the two systematic reviews. The details of the search terms

and inclusion criteria are provided in Chapters 3 and 4. Generally, peer-reviewed articles of observational studies published in English were selected. Flow charts of the study selection process based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were provided in both chapters. The following variables were retrieved from the included articles: authors, year of publication, country of study, year of data collection, source of data, participants' characteristics (sex, age group, and race/ethnicity), definition of socioeconomic status indicator, and measure of association (odds ratio [OR], RR or HR based on multivariate models along with 95% CI) between socioeconomic status and colorectal cancer related outcomes. The references of all the included studies were checked for potentially relevant studies that were not identified up by the electronic search strategies.

I also assessed the methodological quality and estimated the risk of bias for all included studies. I used the Newcastle–Ottawa scale, which is a quality assessment tool for cross-sectional(85), case-control(86, 87) and cohort studies(86, 87) that focuses on three methodological aspects: selection (representativeness of the sample, sample size, non-respondents, and ascertainment of the exposure), comparability (controlling for confounding factors for cohort and cross-sectional studies and comparing between cases and controls for case-control studies) and measurement (of the outcome for cohort and cross-sectional studies and of the exposure for case-control studies). The maximum score on the Newcastle–Ottawa scale for case-control and cohort studies is nine, while the highest possible score for cross-sectional studies is ten.

For the systematic review of the association between socioeconomic status and risk of colorectal cancer (Chapter 4), I used the ROBINS-I to assess the quality of each study(88).

The ROBINS-I consists of seven bias domains: confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported results. The overall risk of bias was as assigned to one of the four following categories:

- low risk of bias (the study is comparable to a well-performed randomised controlled trial) with a low risk of bias for all domains
- moderate risk of bias (the study appears to provide sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised controlled trial) with a low or moderate risk bias for all domains
- serious risk of bias (the study has some important problems) with a serious risk of bias in at least one domain, but is not at critical risk of bias in any domain
- critical risk of bias (the study is too problematic to provide any useful evidence and should not be included in any synthesis) with a critical risk of bias in at least one domain.

Both review chapters included analysis of the heterogeneity between the included studies. Only cohort and case-control studies were included to the meta-analyses. Cross-sectional studies were excluded because of inexplicitly temporal association between the exposure and the outcome that might introduce the bias to the analyses. A random effects model was used to determine pooled estimates and 95% CIs of the associations. To minimise the heterogeneity between studies, meta-analyses were conducted separately for each of the three socioeconomic status indicators: educational attainment, income and composite socioeconomic status indicator. In addition, the analyses were categorised by screening

modality (FOBT, endoscopy, any screening test or recommended screening) in Chapter 3 and cancer sites (colon, rectal or colorectal) in Chapter 4. Between-study heterogeneity was assessed using the Cochrane Q (χ^2 test) and I^2 statistics. Funnel plots and Egger's tests were used to assess potential publication bias. Subgroup analyses were conducted for country of study, continent of study, year of data collection, year of publication and study design. Sensitivity analyses of the meta-regression assessed the covariates' effect on the pooled result estimates and heterogeneity.

2.3. The model: causal directed acyclic graphs

The complex causal pathways from socioeconomic status to colorectal cancer outcomes were depicted using causal directed acyclic graphs. This method allows a graphical display of the associations suggested by a set of causal assumptions embedded in a narrative description of the hypothesised relationships between the study variables and outcomes(89, 90). The causal diagram depicts the assumed comprehensive causal relationship between exposure and outcome via confounding factors, mediators and colliders(89). The causal diagram also helps the reader to understand the selection bias, information bias and measurement error that are often issues in epidemiological studies(89) and helps the analyst avoid inappropriate modelling.

The outcomes of interest in this research were colorectal cancer screening uptake and risk of colorectal cancer. Causal directed acyclic graphs were drawn separately for each outcome. The causal diagram of socioeconomic disparities in colorectal cancer screening uptake is shown in Figure 2.1. The justification for these proxy measures is that people with higher educational attainment are more likely to have stable employment with higher income. Area of residence (at a very local level) reflects the income of your neighbours,

which is captured by census data and is available for research. Evidence suggests that higher socioeconomic status groups are more likely to have healthy lifestyles with a higher rates of normal body mass index(91-93) and lower rates of smoking(94-101). Figure 2.1 shows that I have assumed that the direction of this association is from socioeconomic status (education or area of residence) to healthy lifestyles rather than vice versa. Studies have also reported that smokers(102-107) and obese adults(108-110) may be less likely to participate in colorectal cancer screening.

In the causal diagram in Figure 2.1, I have assumed that the exposure (educational attainment and area of residence) are proxies for socioeconomic status and the outcome is colorectal cancer screening uptake. The possible mediators of this association (factors via which the exposure affects the outcome) are risky health behaviours (body mass index and smoking). I also assumed that the confounders are age, sex and race because they cause both the exposure (socioeconomic status) and the outcome (colorectal cancer screening uptake). Family history of colorectal cancer is a confounder of the mediators and the outcomes because I assumed that people with a family history of colorectal cancer are more likely to receive healthy behaviour advice more frequently and earlier than the average person because they are more likely to seek clinical advice. People with a family history of colorectal cancer might try to reduce their increased risk of colorectal cancer by reducing body weight and not smoking.

The causal diagram of socioeconomic disparities in risk of colorectal cancer is shown in Figure 2.2. The direction of the association between obesity and smoking and colorectal cancer is likely to be more complex than that for screening uptake. For example, some obese people or smokers might reject offers of health benefits and therefore not participate

in colorectal cancer screening, even if they are invited into the National Bowel Cancer Screening Program. On the other hand, obese people or smokers may realise that they have a higher risk of colorectal cancer due to these risk factors, and they may try to prevent colorectal cancer by taking the screening test. Generally, these risky health behaviours increase risk of colorectal cancer.

The effect of colorectal cancer screening on risk of colorectal cancer also depends on the type of screening modality. Screening by endoscopy can decrease the risk of colorectal cancer by polyp removal. Nevertheless, screening is likely to increase the apparent incidence of colorectal cancer in the population (because of identifying a pool of prevalent colorectal cancers that are still in the asymptomatic phase) in the early stages of the screening program and the incidence will decrease as the screening program matures (and the pool of prevalent cases reduces).

The assumed relationship between socioeconomic disparities in risk of colorectal cancer is shown in Figure 2.2. The pathways are quite similar to the socioeconomic disparities in colorectal cancer screening uptake. However, the outcome is risk of colorectal cancer and the mediators are risky health behaviours and colorectal cancer screening uptake. Age, sex and race are possible confounding factors of the exposure and outcome. Similarly, family history of colorectal cancer is a confounder of the mediator and outcome. I assumed that people with a family history of colorectal cancer have a greater risk of colorectal cancer and they tend to receive healthy behaviour advice more frequently and earlier than the average person because they are more likely to seek clinical advice. People with a family history of colorectal cancer might try to reduce their increased risk of colorectal cancer by reducing body weight and not smoking.

The diagrams below demonstrate the causal pathways of variables available in the Australasian Colon Cancer Family Registry (ACCFR) and were used in my mediation analyses. For example, awareness, which is a key determinant of health behaviours – affecting the association between socioeconomic status and colorectal cancer outcomes, is not in the diagrams because it was not collected in the Australasian Colon Cancer Family Registry.

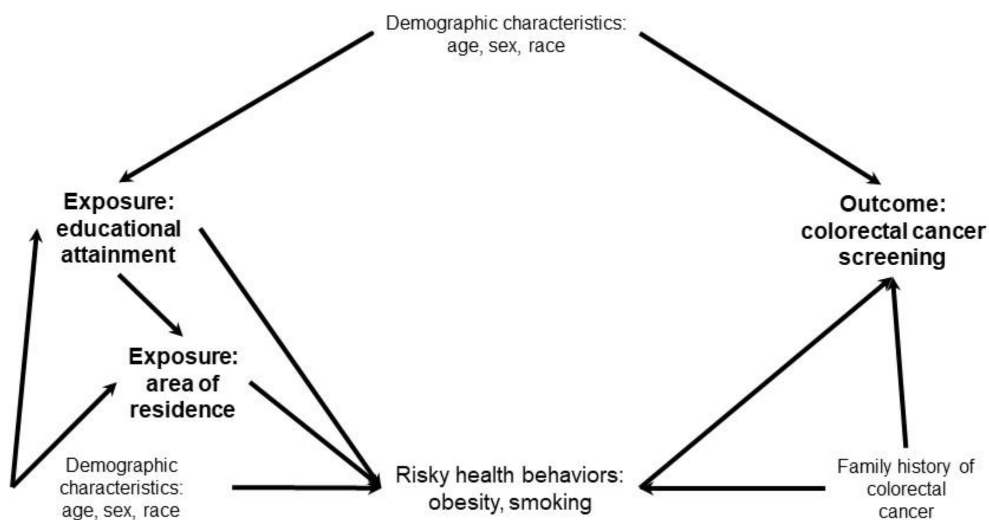


Figure 2.1 Directed acyclic graph of the association between socioeconomic status and colorectal cancer screening uptake that is mediated by smoking, and obesity.

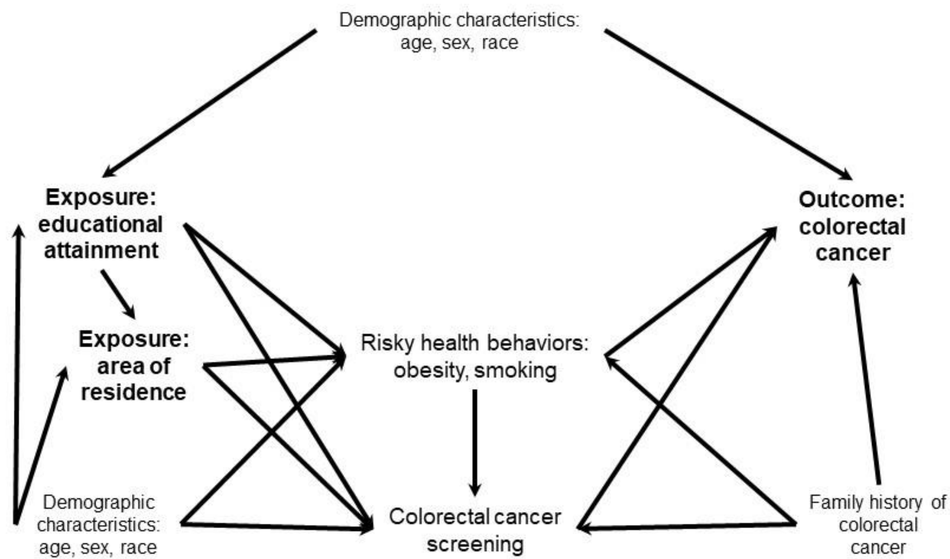


Figure 2.2 Directed acyclic graph of the association between socioeconomic status and colorectal cancer risk that is mediated by colorectal cancer screening uptake, smoking, and obesity.

2.4. The data: Australasian Colon Cancer Family Registry

The Australasian Colon Cancer Family Registry was used in the mediation analyses (Chapters 5 and 6). The Australasian Colon Cancer Family Registry is a large population-based case-control family cohort that was designed to study colorectal cancer aetiology[111]. In brief, participants were recruited via population-based case and control probands. Case probands were residents of the Melbourne metropolitan area who were diagnosed between 1997 and 2007 with an incident first primary adenocarcinoma of the colon or rectum between 18 and 59 years of age and registered to the Victorian Cancer Registry. Attempts were made to recruit the case probands' adult first- and second-degree relatives as well as their spouses or partners. In addition, all first-degree relatives of any participant with a diagnosis of colorectal cancer were sequentially ascertained. Population

control-probands that were frequency matched to the age and sex of the case probands and living in the Melbourne metropolitan area, were identified from the federal electoral roll. As for the case probands, attempts were made to recruit the first- and second-degree relatives of control probands. The focus of this thesis is the population-based Australasian Colon Cancer Family Registry participants from both case and control families, to be able to infer the results to the average risk of colorectal cancer in Australians.

The outcomes for the mediation analyses were colorectal cancer screening (Chapter 5) and colorectal cancer risk (Chapter 6). The Australasian Colon Cancer Family Registry recruited colorectal cancer case-probands from the Victorian Cancer Registry. In this analysis, the colorectal cancer cases were the Australasian Colon Cancer Family Registry participants who were diagnosed on or after the date of having their first screening test uptake or at any time if they did not do the colorectal cancer screening test. For colorectal cancer screening uptake, the screening modality (FOBT, sigmoidoscopy and colonoscopy) and their details were collected. Colorectal cancer screeners were defined as the Australasian Colon Cancer Family Registry participants who had ever screened by FOBT or sigmoidoscopy or colonoscopy because of their family history of colorectal cancer or routine or yearly exam or check-up.

The main exposures for both mediation analysis chapters were educational attainment and the Index of Relative Socioeconomic Disadvantage (IRSD). The Australasian Colon Cancer Family Registry collected educational attainment in the categories: primary school, year 7 or 8, year 9 or 10, year 11 or 12, vocational training, started but did not graduate from university, and graduated from university. IRSD is a composite socioeconomic status indicator based on area of residence and defined by participants'

residential postcode. This is a part of the Census of Population and Housing: Socio-Economic Indexes for Areas (SEIFA)[112]. The IRSD is based on core variables of socioeconomic status (income, education and occupation), direct measures of disadvantage (wealth, assets, employment status, residential condition and language disadvantage) and reflect measures of disadvantage (indigenous status). I linked the participants' postcode to the SEIFA database for 2001 because of the concurrent data collection timeframes for the census and the Australasian Colon Cancer Family Registry. The IRSD from SEIFA 2001 were categorised in quintiles based on the distribution in each state.

Potential mediators in this analysis were colorectal cancer screening uptake, body mass index and pack-years of smoking. Colorectal cancer screening uptake was defined as mentioned above. Body mass index was calculated by weight in kilograms divided by height in metres squared. For smoking, pack-years of smoking was calculated by the number of packs of cigarettes (20 cigarettes per pack) per day multiplied by number of years of smoking. Age, sex and family history of colorectal cancer were the confounding factors available in the Australasian Colon Cancer Family Registry employed in the causal diagrams.

The Australasian Colon Cancer Family Registry is a family-based cohort. Therefore, relatives with no previous diagnosis of colorectal cancer are more likely to screen (due to awareness) compared to the general population. Additionally, the relatives have higher risk of developing colorectal cancer (because of their family history of colorectal cancer) than the general population. Therefore, I included the Australasian Colon Cancer Family Registry participants aged 40 years and older instead of aged 50 years and older in

Chapter 5. Correspondingly, I included all of the Australasian Colon Cancer Family Registry participants (aged 18 years and older) to the analyses of Chapter 6.

2.5. The analytic method: mediation analysis

Mediation analysis aims to identify and quantify the direct effect from an exposure (independent variable) to an outcome (dependent variable) and the indirect or mediated effect via a mediator (intermediate variable). Mediation analysis has been used for a few decades especially in the social sciences. Mediation analysis is now increasingly used in social epidemiology to investigate how socioeconomic factors contribute to the health of populations(73). It not only demonstrates complex causal pathways from socioeconomic status to health outcome(89) but also estimates the magnitude of the effect from an exposure via a mediator to a health outcome. There is much evidence of socioeconomic disparities in health, but improving socioeconomic status is unlikely to be practical in public health. Instead, interventions on a possible mediator will minimise the effect of socioeconomic disparities (indirectly via the mediator) on the health outcome.

A mediator occurs in a causal pathway from an exposure to an outcome. The mediator causes variation in the outcome and is caused by the exposure(113, 114). A direct effect shows the exposure effect on the outcome at a fixed level of the mediator(115). An indirect effect represents the effect of exposure on the outcome that operates through mediators(115). The total effect is the overall effect of the exposure on the outcome(115).

Steps to establish mediation by Baron and Kenny(116) have had a huge influence in mediation analysis. The Baron and Kenny approach consists of series of statistical tests that are simplified to three logistic equations $(i)-(iii)$(117). The exposure (X) must affect

the outcome (Y), as represented by coefficient c in equation (i). The exposure (X) must affect the mediator (M), as represented by coefficient a in equation (iii). The mediator (M) must affect the outcome (Y) when the exposure (X) is controlled, as represented by coefficient b in equation (ii). Lastly, the direct effect, coefficient c' in equation (ii), must be nonsignificant.

$$Y = i_1 + cX + e_1 \quad (i)$$

$$Y = i_2 + c'X + bM + e_2 \quad (ii)$$

$$M = i_3 + aX + e_3 \quad (iii)$$

The mediated effect from this approach is the product of coefficients a and b and is referred to as product methods(118). The causal steps to establish mediation by Baron and Kenny are relatively simple but I did not adopt this approach in this thesis because they have issues related to: inconsistent mediation where the relationship between the exposure and the outcome may be nonsignificant because of the opposite directions of the direct and indirect effects(117); partial mediation(117); low power to detect the mediated effect(119); and no numerical estimates of the strength of the mediated effect(119). The other limitations of traditional Baron and Kenny approach to mediation analysis are concerns about the extended definitions and results of direct and indirect effects in models with interactions and non-linearities, and the importance of articulating conditions for a causal interpretation, especially for confounders of the mediator and outcome factors(120-122). For these reasons, I adopted the causal inference under counterfactual approach to deal with more complex models with several confounders instead of the Baron and Kenny approach.

The counterfactual framework for causal inference was first described by Hume in 1748. Neyman provided a formal notation in 1923, which was later further developed by Rubin(123, 124). The framework-related graphical representation of causality was established by Pearl(121, 125). The counterfactual framework rests on potential outcomes that cannot be observed(120, 126) Outcomes of a subject are considered in two sets of circumstances. The first circumstance is the observed circumstance of the subject (factual circumstance) that causes the observed outcome. The other is the counterfactual circumstance that, contrary to fact, did not occur(120, 126). The counterfactual circumstance causes the potential outcome that cannot be observed. Since VanderWeele and Vansteelandt(127, 128) developed the notations of direct and indirect causal effects from causal inference in the counterfactual framework(120, 121), the counterfactual framework for causal inference has become more widely adopted.

The outcomes from the counterfactual framework for causal inference are direct and indirect effects. These effects are estimated from regression parameters if certain assumptions (no confounding factors) hold and the models are correctly specified. If there is no interaction between the exposure and the mediator, the direct and indirect effects from the counterfactual approach are the same as those of the Baron and Kenny approach(115, 117). The natural indirect effect (NIE) expresses how much the outcome would change on average with no exposure(129) or with exposure(118) and changing mediator to whatever value it would attain for each individual under the condition of having exposure(118, 129). The natural direct effect (NDE) demonstrates how much the outcome would change if the exposure were changed but the mediator were kept at the level at which it would be if each individual received no exposure(118, 129). The controlled direct effect indicates how much the outcome changes on average if the exposure is

changed and the mediator is kept constant over the entire population[118, 129]. The controlled and natural direct effects are similar, except when there is an interaction between the exposure and mediator. In that case, the natural direct effect is likely to be the average of the controlled direct effects, whereas the controlled direct effect depends on the level of the mediator[121].

In practice, the controlled direct effect is the most relevant metric for policy evaluation[121, 130]. The controlled direct effect shows the direct effect of an exposure on an outcome when the effects of mediators are kept constant. On the other hand, the natural direct and indirect effects are more suitable for the identification of aetiology mechanisms[130]. They allow the decomposition of the total effect. The total effect is the sum of the natural direct and indirect effects, even if there is an interaction between exposure and mediators[73]. The aim of my thesis was to explore the causal pathway between socioeconomic disparities and colorectal cancer outcomes via health behaviours, and therefore my thesis focuses on the natural direct and indirect effects. The other application of the decomposition of the total effect is the possibility of calculating the proportion mediated as the ratio of the natural indirect effect to the total effect. This reflects how much the effect of an outcome would change if the pathway from the exposure to the mediators is prevented[115]. In practical, the proportion mediated is calculated by using the formula $100\left(\frac{lnOR_{NIE}}{lnOR_{NDE}+lnOR_{NIE}}\right)$[131]. Nevertheless, the proportion mediated has two main limitations. Firstly, the proportion mediated is dramatically affected by variables included in the analysis[117] and its CI is usually wide. Instead of using the CI of the mediated proportion to represent the mediated effect, the CI of the natural indirect effect is the better representative. Secondly, the interpretation of the proportion mediated can be

problematic. For example, it can be over 100 percent when natural direct and indirect effects go in opposite directions[115].

For causal interpretation of the natural direct and indirect effects, four assumptions are required[115, 118]: (a) no unmeasured confounder of the exposure–outcome relationship, (b) no unmeasured confounder of the mediator–outcome relationship, (c) no unmeasured confounder of the exposure–mediator relationship and (d) no mediator–outcome confounder that is affected by the exposure. Additionally, an assumption of temporal ordering that assumes that the exposure occurs before the mediator, and that they both precede the outcome is essential for assumptions (a), (b) and (c). If the assumption of temporal ordering is not satisfied, the results of the analysis do not represent a causal effect[118]. Generally, randomisation can deal with exposure–outcome and exposure–mediator confounding factors. However, the randomisation is unlikely to have an effect on the mediator and the mediator–outcome confounding factors can still be an issue and a limiting factor for causal interpretation. That is a key limitation of traditional mediation analysis based on Baron and Kenny's approach.

In this thesis, the mediation analyses used the Australasian Colon Cancer Family Registry, which is an observational dataset. Therefore, the confounding factors are the main concern that should be taken into account to minimise bias. However, controlling for confounding factors was limited by the variables collected by the Australasian Colon Cancer Family Registry and there are unknown confounders that I cannot adjust for. Therefore, sensitivity analysis was used to investigate how robust the results are to the violation of those identification assumptions.

There are several techniques of sensitivity analysis such as the binary confounder method, correlated residuals method and left-out variables error[132]. The correlated residual method by Imai[133, 134] was applied in this thesis because it is based on regression and can be performed with standard statistical software such as Stata[135] or R[136]. Imai[133] re-wrote the assumptions (no unmeasured exposure–outcome, exposure–mediator and mediator–outcome confounders) to the sequential ignorability assumption, which consists of two parts. Firstly, for the observed pre-exposure confounding factors, the exposure assignment is assumed to be ignorable (i.e. statistically independent of potential outcomes and potential mediators). Secondly, the mediator is ignorable given the observed exposure and pre-exposure confounders. This implies the randomisation of the mediator. This second part is referred to as nonrefutable because it cannot be directly investigated from the observed data. Sensitivity analysis is a method for probing the possibility of a nonrefutable assumption[133]. The aim of a sensitivity analysis is to quantify if and to what degree the sequential ignorability assumption has been violated. The sensivity parameter is ρ, which is the correlation between the error for the mediation model and the error for the outcome model[132, 133, 135]. Under the sequential ignorability assumption, ρ is zero. If there is any omitted variable that affects both the mediator and the outcome variables, the omitted variable is part of the two error terms; therefore, the value of ρ will increase, which reflects departure from the sequential ignorability assumption. When the sequential ignorability assumption is unlikely to be satisfied, the range of sensitivity parameter ρ and the mediated effect are $(-1, 1)$ and $(-\infty, \infty)$, respectively[132]. However, there is no absolute threshold for ρ to indicate a problematic level of susceptibility of the results to confounding[132, 133].

Imai et al[133, 134, 137] developed the Stata mediation analysis package[135] based on a counterfactual approach and the sequential ignorability assumption. The package simulates the predicted values of the mediator or outcome variable, which are not observed, and calculates the average causal mediation, direct and total effects (*medeff* command). The uncertainty estimates are based on the quasi-Bayesian Monte Carlo approximation[135]. The sensitivity analysis uses the *medsens* command, which indicates how robust the results are to the violation of the sequential ignorability assumption, and gives not only ρ but also plots the estimated average mediated effect as ρ increases. There were two main reasons why the Stata mediation package was used in this thesis. Firstly, the Australasian Colon Cancer Family Registry is an observational study that is likely to have issues with confounding factors. Therefore, the sensitivity analysis command is useful to quantify the magnitude of any sequential ignorability assumption violation. Secondly, the command has the *vce* option that selects a specific type of standard error. The Australasian Colon Cancer Family Registry is a large family study, which means that participants can be members of the same families. To minimise collinearity within families, all analyses included a cluster subcommand to account for non-independence of relatives in the sample.

The *paramed* command for performing causal mediation analysis using parametric regression models was also adopted in this thesis to confirm the mediated effect. The *paramed* command is also based on the counterfactual approach and regression model[118, 138]. It estimates ORs for the natural direct effect, the natural indirect effect and total effect with standard errors and CIs derived using the delta method[138]. The *paramed* command is flexible for several types of outcomes and mediators. However, it does not have the

option to perform sensitivity analysis to investigate the violation of the sequential ignorability assumption.

Chapter 3. Socioeconomic Status and Colorectal Cancer Screening Practices: A Systematic Review and Meta-analysis

3.1. Introduction

Colorectal cancer is a major cause of disease burden in high-income countries[139]. In 2015, colorectal cancer was the third most commonly diagnosed malignancy and second cause of cancer death for men and women globally[140]. Studies have consistently shown that people in the most deprived population groups are at higher risk of and experience higher morbidity and mortality from colorectal cancer[141, 142]. Mortality from colorectal cancer can be reduced if the disease is detected and treated at an early stage or if the lesions that precedes most colorectal cancers are detected and removed before becoming malignant. Over the last two decades, experimental and observational studies have consistently demonstrated the effectiveness of several screening modalities – mainly FOBT[21-25], flexible sigmoidoscopy[26-29] and colonoscopy[143, 144] – in reducing colorectal cancer mortality. These studies provided the evidence base for numerous clinical guidelines and led many countries to establish national screening programs[46, 145-148]. Despite important discrepancies in the recommended procedures and the timing and frequency of screening, a large consensus exists among clinicians and health policymakers about the health benefits of regular colorectal cancer screening. To achieve those health benefits and the full preventive potential of screening, the level of participation in the population must be as high as possible. Since the introduction of

colorectal cancer screening, however, low uptake rates have been a common and important challenge to colorectal cancer prevention and are a major barrier to the full effectiveness of screening initiatives. In most countries with a colorectal cancer screening program – whether organised or opportunistic – less than half of the targeted population agree to screen[149, 150].

The determinants of colorectal cancer screening behaviour have been extensively investigated[151-155] and socioeconomic status has been identified as a strong predictor of screening participation. Several studies conducted in healthcare systems using organised or opportunistic approaches to colorectal cancer screening have consistently shown low screening participation among those in the lowest socioeconomic groups of the population[156-159]. However, earlier reviews[152-155] did not provide the overall estimated magnitude of the association among the studies. In such a context, where deprived populations experience both higher colorectal cancer morbidity and mortality and lower screening uptake rates, the implementation of screening programs might reinforce and widen the existing inequities between socioeconomic groups in terms of colorectal cancer outcomes[160, 161].

The main objectives of this study were to provide a comprehensive overview of the published literature on colorectal cancer screening and socioeconomic status and to quantify the magnitude of the association between screening participation and socioeconomic status indicators for specific screening modalities.

3.2. Methods

3.2.1. Search strategy and study selection

Embase, MEDLINE, PsycINFO and the Cochrance library databases, up to June 2017, were searched to identify observational studies investigating the association between colorectal cancer screening and socioeconomic status. The following combinations of search terms were used: colorectal neoplasms (MeSH) or colorectal cancer$.mp. or CRC.mp. or colorectal neoplasm$.mp. or colon cancer$.mp. or colon neoplasm$.mp. or colonic neoplasm$.mp. or colonic cancer$.mp. or rectal neoplasm$.mp. or rectal cancer$.mp. or bowel cancer$.mp. and mass screening (MeSH) or screening.mp. and socioeconomic factors (MeSH) or education (MeSH) or ethnic groups (MeSH) or health status disparities (MeSH) or social determinants of health (MeSH) or social determinants$.mp. The search was limited to peer-reviewed articles published in English.

All observational study designs were eligible for inclusion in the systematic review. To be included, studies had to explicitly state that the procedures considered in the analysis were performed on asymptomatic persons for screening purposes. Studies reporting on procedures conducted to investigate clinical symptoms and studies for which the distinction between screening and diagnostic tests could not be made were excluded. Measures of association between socioeconomic status and colorectal cancer screening uptake had to be based on multivariate models and reported as adjusted ORs, RRs or HRs along with 95% CIs.

3.2.2. Data extraction and quality assessment

The following information was extracted for all the included studies: first author's name, year of publication, country of study, study design, source of data, participants' characteristics, colorectal cancer screening test used, percentage of the screening uptake, socioeconomic status indicators, measure of association with the corresponding 95% CI and factors adjusted for in the multivariable model. The references of the included studies were checked for articles fulfilling the review's inclusion criteria. The quality of the included studies was evaluated with the Newcastle–Ottawa scale, a quality assessment tool designed for case-control, cohort(86, 87) and cross-sectional studies(85). The scale consists of three qualitative dimensions: selection (representativeness of the sample, sample size, non-respondents, and ascertainment of the exposure), comparability (controlling for confounding factors for cohort and cross-sectional studies and comparing between cases and controls for case-control studies), and measurement (outcome for cohort and cross-sectional studies and exposure for case-control studies). The maximum score on the Newcastle–Ottawa scale is nine for case-control and cohort studies, while the highest possible score for cross-sectional studies is ten.

3.2.3. Data synthesis and statistical analysis

Colorectal cancer screening modalities were categorised into four groups:

- FOBT – any test that examines the presence of blood in stool
- endoscopy – sigmoidoscopy or colonoscopy or both
- any screening test–FOBT, sigmoidoscopy or colonoscopy

- recommended screening – any screening routine based on published guidelines.

Socioeconomic status indicators considered in this review include: educational attainment, income, and composite socioeconomic status indicators (i.e. the Townsend Material Deprivation Index and the Scottish Index of Multiple Deprivation). I defined income as individual income, family income and poverty level. The composite socioeconomic status indicator based on area of residence is an indicator that combines a variety of neighbourhood-level variables (such as unemployment and housing) into a single quantity[114, 162]. Given the variability of the socioeconomic status indicators varied across studies, the comparison of colorectal cancer screening uptake in the highest socioeconomic status groups (highest educational attainment or highest income or least deprived) to that in the lowest socioeconomic status categories (reference category) was the only measure of association used in this analysis. For example, an OR of less than one is indicative of highest socioeconomic status group having a lower screening uptake, and an OR of greater than one indicative of highest socioeconomic status group having a higher screening uptake.

Meta-analyses of observational studies present particular challenges because of: the inherent biases of observational data; and the specific biases associated with the various designs (such as cohort, case-control, cross-sectional and ecological study)[163, 164].

Combining effect estimates of observational studies might be appropriate for all studies, for a subgroup of studies, or not appropriate at all. Researchers have provided different reasons for pooling or not pooling data and opinions differed on how to approach this question and how the decision should be made[165]. Dekkers et al recommended to take into account study diversity, sensitivity, risk of bias and heterogeneity when deciding for

or against pooling estimates[166]. To date, there is still no consensus on how to conduct meta-analyses of observational studies[165].

I acknowledged the risk of bias and limitations mentioned above and the fact that combining different study designs in a meta-analysis can result in misleading findings if done without careful consideration. For this review, however, I decided to conduct a meta-analyses stratified by study designs bases on: (i) a careful assessment of the quality and risk of bias of the included studies and their heterogeneity; (ii) the lack of data and relevant studies; (iii) the need to answer the research question of this systematic review between of following the recommendation.

To handle dependency among effect size estimates for studies reporting multiple measures of association – based, for example, on subgroup analysis of sex, age group, ethnicity, year of data collection etc. – a pooled estimate was calculated for each study. Therefore, each study included in the meta-analysis provided only one measure of association. Meta-analyses were conducted separately for each pair of the four colorectal cancer screening modalities and three socioeconomic status indicators. A random effects model was used to calculate pooled estimates and 95% CIs of the probability of screening participation based on the results of the multivariable models reported in the included studies. Between-study heterogeneity was assessed using the Cochrane Q (χ^2 test) and I^2 statistics. Funnel plots and Egger's test were used to assess potential publication bias. Subgroup analyses were conducted including age group, year of data collection or publication, country of participants recruitment, and race or ethnicity. Sensitivity analyses of meta-regression were performed to assess the covariates effect on the pooled result estimates and accompanying heterogeneity.

3.3. Results

3.3.1. Study selection

The literature search identified 1,144 studies. I excluded: 1,083 non-relevant studies, 20 studies which did not provide any measure of association and 95% CI, six studies that did not present screening purpose, and four studies that measure of association of socioeconomic status in continuous scale (Figure 3.1). Overall, 30 cross-sectional studies and one retrospective cohort study[(167)] met the inclusion criteria.

3.3.2. Study characteristics

These studies were published between 1998 and 2016 and were conducted in ten different high-income countries. Twenty-two studies were from the United States[(167-188)], and of these, 11 focused on the following minority populations: African Americans[(168, 174, 175, 183)], Latinos[(172)] and immigrants[(176, 178-180, 183, 185)]. Three studies reported on colorectal cancer screening uptake for men[(175)] and women[(168, 178)] separately. Three studies[(172, 176, 189)] included people aged under 50 years; the other studies analysed screening in people aged 50 years and over (Table 3.1). Most studies (77.4%) used self-reported assessment of screening practices. The remaining studies used Medicare records (9.7%)[(167, 169, 171)], medical records (6.5%)[(190, 191)] and national bowel cancer screening records (3.2%)[(192)].

Educational attainment was the most commonly used indicator of people's socioeconomic status[(168-179, 181-186, 188, 189, 193-197)], followed by income[(170, 171, 173, 174, 177, 179-182, 184-187, 194)] and composite socioeconomic status indicators[(167, 190-192)]. Twelve studies used both educational attainment and income as their socioeconomic status indicators[(170, 171, 173, 174, 177, 179, 181, 182, 184-186, 194)].

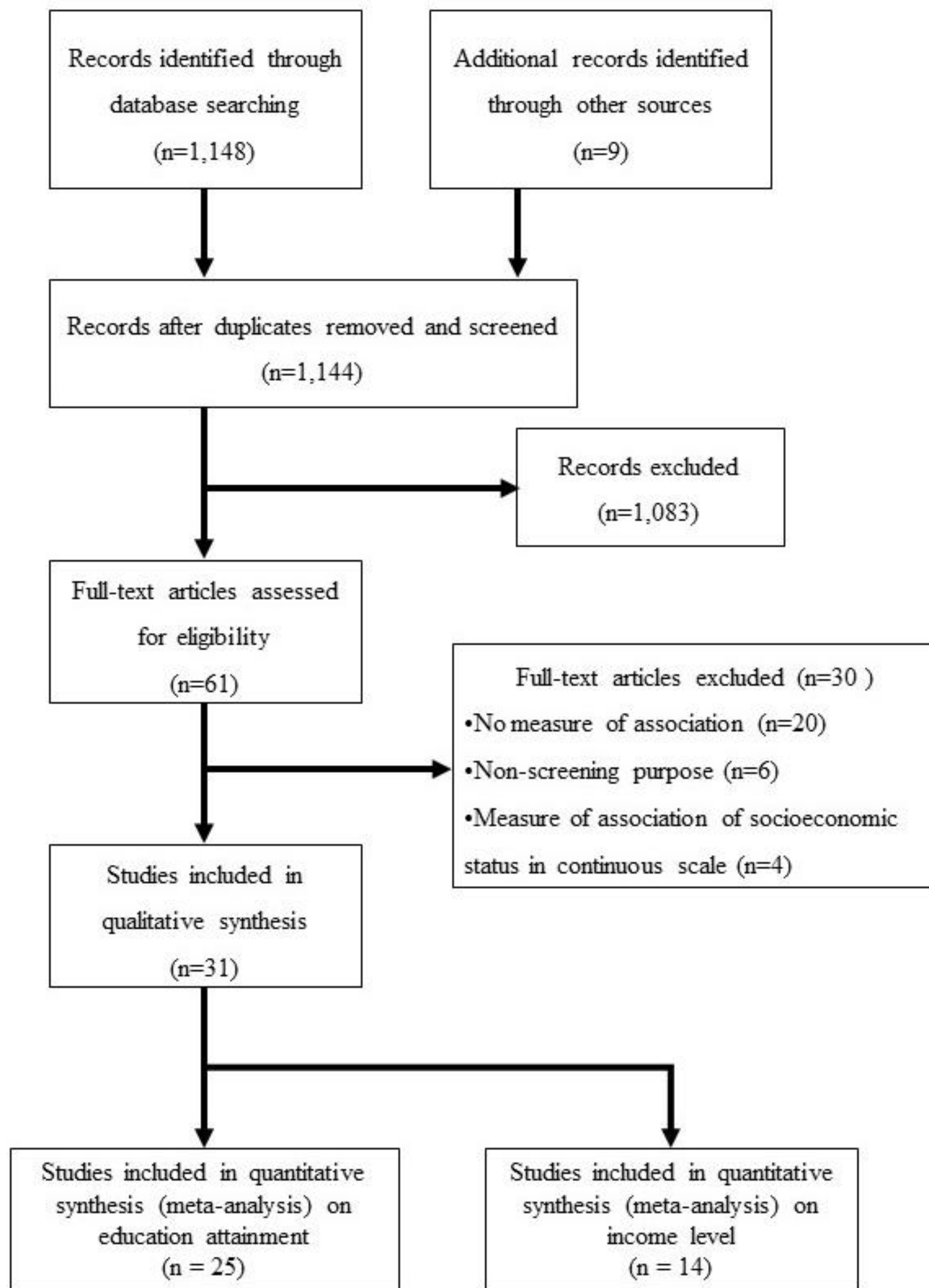


Figure 3.1 Flow chart of study selection process.

In terms of screening modalities, 48.4% assessed endoscopy[167-169, 171, 172, 174, 175, 179, 180, 183, 184, 187, 188, 196, 198], 38.7% of the studies assessed FOBT uptake[171, 172, 175, 176, 179, 188, 192-197] and 32.3% reported on any screening test[169, 170, 173, 175, 178, 186, 188, 190, 191, 196]. Five studies reported on screening uptake based on guideline recommendations[177, 181, 182, 185, 189]. Characteristics of the studies are presented in Appendix A table 1−3. The median percentage of any screening test uptake (10 studies) was 40.4% with a range of 18.3%–76.3%. The median percentage of the screening uptake (range) of endoscopy (14 studies), FOBT (12 studies), and tests based on guideline recommendations (5 studies) were 40.3% (7.7%–62.6%), 16.0% (8.2%–61.0%), and 59.6% (4.5%–71.2%), respectively.

The average score on the Newcastle–Ottawa scale for the 30 cross-sectional studies was 6.3 out of a maximum possible score of ten (range: 4 to 9). The only cohort study included had a score of 8 out of maximum score of 9. Further details of the quality assessment of the included studies are presented in Table 3.1.

Table 3.1 Characteristics of studies included in qualitative synthesis (n=31)

Author, year	**Country of participants recruitment**	**Source of data**	**Sex-specific analyses**	**Target age group**	**Race/ Ethnicity#**	**Socioeconomic status indicators (exposure)**	**Screening modality (% screening uptake) (outcome)**	**Newcastle–Ottawa scale score**
Halbert, 2016[174]	United States	The Behavioural Risk Factors Surveillance Survey 2010 (n=262)	Combined	50–75	African Americans	Education and income (area of living)	Endoscopy (57.0%)	• Selection: 1 • Comparability: 2 • Measurement: 2
Meyer, 2016[181]	United States	The Behavioural Risk Factors Surveillance Survey 2012 (n=57,002)	Combined	60–64 & 66–70	Non-specific	Education and income (household)	U.S. Preventive Services Task Force guideline (71.2%)	• Selection: 3 • Comparability: 2 • Measurement: 2
Solmi, 2015[197]	United Kingdom	The population-based English Longitudinal Study of Aging 2010/11 (n=1,833)	Combined	61–69	Non-specific	Education	FOBT (61.0%)	• Selection: 2 • Comparability: 2 • Measurement: 2
Kobayashi, 2014[195]	United Kingdom	The population-based English Longitudinal Study of Aging 2010/11 (n=3,078)	Combined	60–75	Non-specific	Education	FOBT (55.0%)	• Selection: 3 • Comparability: 2 • Measurement: 2
Liss, 2014[177]	United States	The Behavioural Risk Factors Surveillance Survey 2010 (n=226,546)	Combined	50–75	Non-specific	Education and income (household)	U.S. Preventive Services Task Force guideline (59.6%)	• Selection: 3 • Comparability: 2 • Measurement: 2
Menon, 2014[180]	United States	The South Asian Health Descriptor Study in Chicago and Illinois 2009 (n=275)	Combined	≥50	South Asians	Income (Individual)	Endoscopy (16.9%)	• Selection: 1 • Comparability: 2 • Measurement: 2

Author, year	Country of participants recruitment	Source of data	Sex-specific analyses	Target age group	Race/ Ethnicity#	Socioeconomic status indicators (exposure)	Screening modality (% screening uptake) (outcome)	Newcastle–Ottawa scale score
Oluyemi, 2014[182]	United States	The Behavioural Risk Factors Surveillance Survey 2006 (n=155,020), 2008 (n=197,969) and 2010 (n=229, 202)	Combined	50–75	Non-specific	Education and income (individual)	U.S. Preventive Services Task Force guideline (59.0%–65.0%)	• Selection: 2 • Comparability: 2 • Measurement: 2
Ryu, 2014[185]	United States & South Korea	2009 California Health Interview Survey for Korean Americans (n=519) and Korean National and Nutrition Examination 2009 (n=3,532)	Combined	≥50	Korean Americans and Koreans	Education and income(household)	U.S. Preventive Services Task Force guideline (60.4%) and Guideline (37.1%)	• Selection: 3 • Comparability: 2 • Measurement: 2
López-Charneco, 2013 [196]	Puerto Rico	The Puerto Rico Behavioural Risk Factor Surveillance System 2008 (n=2,920)	Combined	≥50	Non-specific	Education	Any screening test (42.3%), endoscopy (39.8%) and FOBT (8.2%)	• Selection: 2 • Comparability: 2 • Measurement: 2
Mansouri, 2013[192]	Scotland	The Scottish Bowel Screening Program people who registered with the General practitioner in Greater Glasgow and Clyde (n=394,117)	Combined	50–74	Non-specific	The Scottish Index of Multiple deprivation	FOBT (52.0%)	• Selection: 4 • Comparability: 2 • Measurement: 3
Doubeni, 2012+[167]	United States	A cohort study of members of Reliant Medical Group/Fallon Community Health Plan in Massachusetts, Kaiser Permanente Georgia, or Lovelace Health System in New Mexico (n=100,566)	Combined	50–74	Non-specific	Neighbourhood socioeconomic status	Endoscopy (11.0%)	• Selection: 4 • Comparability: 2 • Measurement: 2
Greene, 2012[173]	United States	The 5 public health regions in Arkansas 2006 (n=2,092)	Combined	≥50	Non-specific	Education and income (household)	Any screening test (51.45)	• Selection: 3 • Comparability: 2 • Measurement: 2

Author, year	Country of participants recruitment	Source of data	Sex-specific analyses	Target age group	Race/ Ethnicity#	Socioeconomic status indicators (exposure)	Screening modality (% screening uptake) (outcome)	Newcastle–Ottawa scale score
Hall, 2012[175]	United States	The Prostate Cancer Risk Assessment Program 2010 (non-specific race: n=135 and African Americans: n=204)	Male	≥50	Non-specific and African Americans	Education	Any screening test (66.2%–76.3%), endoscopy (44.1%–58.5% and FOBT (49.0%–60.7%)	• Selection: 2 • Comparability: 2 • Measurement: 2
Ouakrim, 2012[189]	Australia	The Australasian Colorectal Cancer Family Registry 1997–2001 (n=1,627)	Combined	≥18	Non-specific	Education	Guideline (4.5%)	• Selection: 3 • Comparability: 2 • Measurement: 2
Patel, 2012[183]	United States	The Meharry Medical College Community Health Centres-Community Networks Program 2005 (n=460)	Combined	≥50	African Americans	Education	Endoscopy (35.0%)	• Selection: 1 • Comparability: 2 • Measurement: 2
Richard, 2011[184]	United States	The Community Health Survey of the New York city Department of Health and Mental Hygiene 2003 and 2007 (n=18,358)	Combined	≥50	Non-specific	Education, income (area of living) and income (household)	Endoscopy (51.7%)	• Selection: 2 • Comparability: 2 • Measurement: 2
Wilf-Miron, 2011[191]	Israel	Maccabi Healthcare Services adult members who visited their general practitioner at least once during the previous two years (2008) (n=303,330)	Combined	51–74	Non-specific	Socioeconomic rank	Any screening test (27.5%)	• Selection: 3 • Comparability: 2 • Measurement: 3
Adams-Campbell, 2010[168]	United States	Black Women's Health Study 1995 (aged 50-59 years old: n=6,836 and age ≥60 years old: 2,757)	Female	50–59 and ≥60	African Americans	Education	Endoscopy (aged 50-59 years old: 61.3% and age ≥60 years old: 62.6%)	• Selection: 1 • Comparability: 2 • Measurement: 2
Frederiksen, 2010[194]	Denmark	Two counties of Copenhagen and Vejle August 2005 to December 2006 (n=173,670)	Combined	50–74	Non-specific	Education and income (household)	FOBT (48.0%)	• Selection: 3 • Comparability: 2 • Measurement: 3

Author, year	Country of participants recruitment	Source of data	Sex-specific analyses	Target age group	Race/ Ethnicity[#]	Socioeconomic status indicators (exposure)	Screening modality (% screening uptake) (outcome)	Newcastle–Ottawa scale score
Pornet, 2010[190]	France	The campaign of colorectal cancer screening in the department of the Calvados June 2004 to June 2006 (n=8,691)	Combined	50–74	Non-specific	Townsend index	Any screening test (38.4%)	• Selection: 5 • Comparability: 2 • Measurement: 1
Dimitrakaki, 2009[193]	Greece	The national household survey Hellas Health I 2006 (male: n=483, female: n=552)	Male and female	50–69	Non-specific	Education	FOBT male:10.9%, female: n=8.3%)	• Selection: 3 • Comparability: 2 • Measurement: 2
Doubeni, 2009[171]	United States	Colorectal cancer–free noninstitutionalized beneficiaries who were enrolled at the beginning of the 2000 (n=8,355) and 2005 (n=7,646) survey years.	Combined	65–80	Non-specific	Education and income (household)	Endoscopy (2000: 41.0% and 2005: 47.5%) and FOBT (2000: 14.8% and 2005: 10.5%)	• Selection: 3 • Comparability: 2 • Measurement: 2
Walsh, 2009[188]	United States	An intervention trial to increase rates of colorectal cancer screening in Latino and Vietnamese patients at Santa Clara Valley Medical Centre, a public hospital in California 2006 (n=808)	Combined	50–79	Vietnamese	Education	Any screening test (74.0%), endoscopy (23.5%) and FOBT (53.0%)	• Selection: 0 • Comparability: 2 • Measurement: 2
Maxwell, 2008[179]	United States	Filipino American immigrants from 31 community-based organizations in Los Angeles County July 2005 and October 2006 (n=487)	Combined	50–75	Filipino American immigrants	Education and income (individual)	Endoscopy (31.2%) and FOBT (16.0%)	• Selection: 1 • Comparability: 2 • Measurement: 2
Shih, 2008[186]	United States	The National Health Interview Surveys 2000 (n=12,179)	Combined	≥50	Non-specific	Education and income	Any screening test (51.7%)	• Selection: 2 • Comparability: 2 • Measurement: 2
Ananthakrishnan, 2007[169]	United States	The Medicare physician/supplier file and the denominator file of New York, Florida, and Illinois 2002–2003 (n=596,470)	Combined	≥65	Non-specific	Education	Any screening test (18.3%) and endoscopy (7.7%)	• Selection: 3 • Comparability: 2 • Measurement: 3

Author, year	Country of participants recruitment	Source of data	Sex-specific analyses	Target age group	Race/ Ethnicity[#]	Socioeconomic status indicators (exposure)	Screening modality (% screening uptake) (outcome)	Newcastle–Ottawa scale score
Ata, 2006[170]	United States	The National Health Interview Surveys 2000 (n=12,498)	Combined	≥50	Non-specific	Education and income (household)	Any screening test (25.8%)	• Selection: 3 • Comparability: 2 • Measurement: 2
Gorin, 2005[172]	United States	The 2000 National Health Interview Survey adult persons and the Cancer Control Supplement (n=234)	Combined	≥40	Latinos	Education	Endoscopy (20.7%) and FOBT (14.8%)	• Selection: 2 • Comparability: 2 • Measurement: 1
Vlahov, 2005[187]	United States	The New York Cancer Project 2002 (n=5,595)	Combined	≥50	Non-specific	Income (Household)	Endoscopy (40.3%)	• Selection: 2 • Comparability: 2 • Measurement: 2
Maxwell, 2000[178]	United States	Filipino (n=218) and Korean (n=229) immigrants who used community-based social service organizations or two church congregations	Female	≥50	Filipino immigrants	Education	Any screening test (Filipino immigrants: 25.0% and Korean immigrants: 38.0%)	• Selection: 1 • Comparability: 2 • Measurement: 1
Kim, 1998[176]	United States	Korean Americans who living in the uptown area of Chicago (n=263)	Combined	40–69	Korean Americans	Education	FOBT (9.5%)	• Selection: 2 • Comparability: 2 • Measurement: 1

[#]Race/ ethnicity categories as reported in the publication
[+]Retrospective cohort study

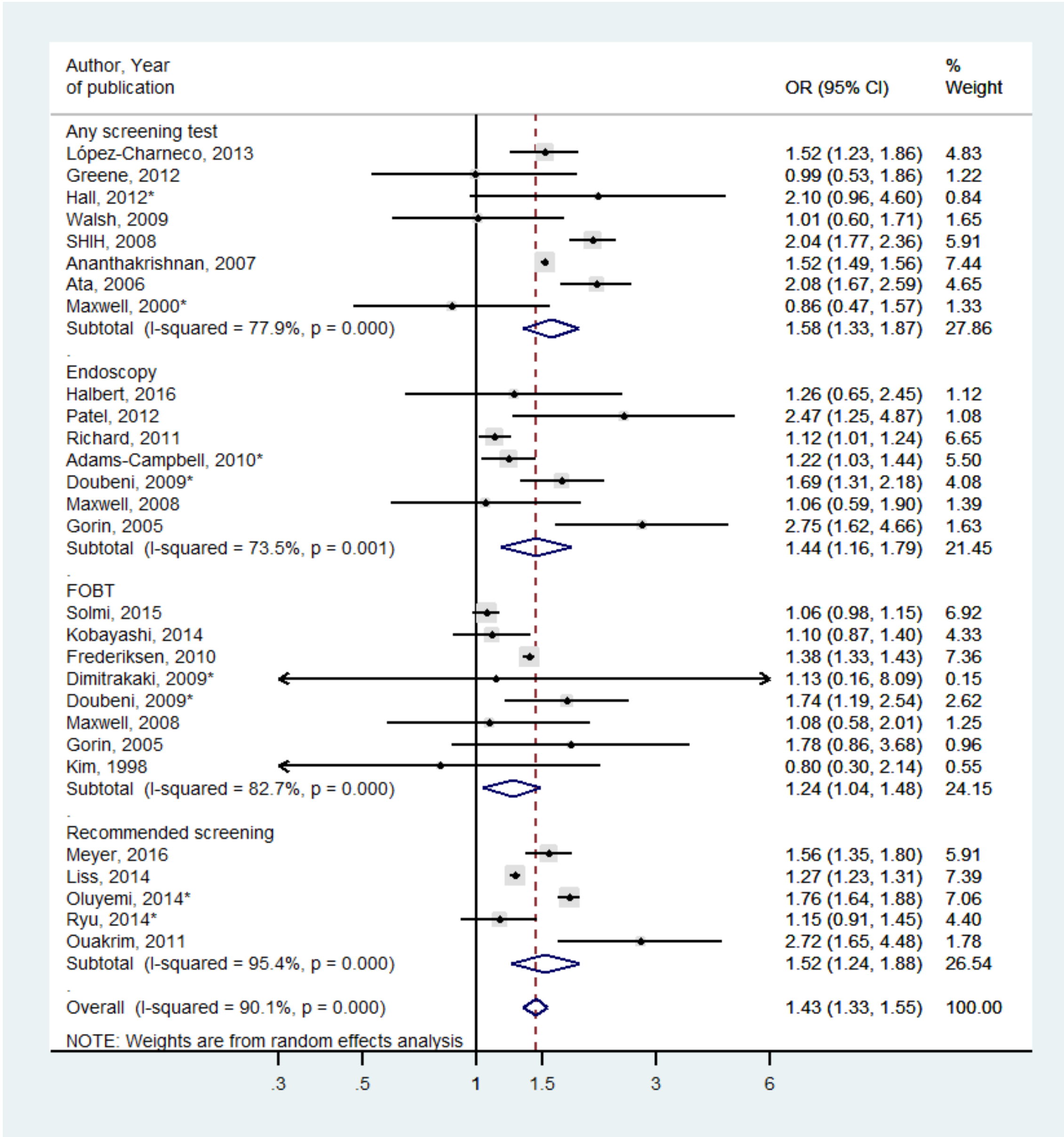
3.3.3. Meta-analyses and publication bias

All measures of the association between socioeconomic status (educational attainment and income level) and colorectal cancer screening uptake were retrieved from cross-sectional studies. There is only a cohort study that demonstrated the association between composite indicators based on area of residence and endoscopy uptake[167].

The individual ORs, pooled estimates and 95% CIs for the associations between educational attainment and colorectal cancer screening of cross-sectional studies are shown in Figure 3.2. Those with the highest educational attainment were, on average, 58% (95% CI 33%, 87%) more likely to engage in colorectal cancer screening (with any test) compared with those with the lowest educational attainment. They were also 44% (95% CI 16%, 79%), 24% (95% CI 4%, 48%) and 52% (95% CI 24%, 88%) more likely to screen with endoscopy, FOBT and recommended screening test, respectively. There was a moderate to high level of heterogeneity between the studies, with I^2 estimates ranging from 73.5% to 95.4%. The subgroup and meta-regression analyses by age group, year of data collection or publication, country of participants recruitment, and race/ ethnicity are shown in Table 3.2. For FOBT, studies conducted in the United States (OR 1.48, 95% CI 1.12, 1.97 and I^2 0.0%) and collected data prior and in 2008 (OR 1.38, 95% CI 1.33, 1.43 and I^2 0.0%) reported that those with the highest level of educational attainment had higher screening uptake. 100.0% of the heterogeneity across all studies of the association between educational attainment and FOBT uptake can be explained by the year of data collection. Moreover, the association between educational attainment and endoscopy uptake of participants aged 50 years old and older (OR 1.32, 95% CI 1.09, 1.58 and I^2 62.7%) and association between educational attainment and recommended

screening uptake of studies collected data prior and in 2008 (OR 2.03, 95% CI 1.36, 3.04 and I^2 65.1%) demonstrated moderate heterogeneity. For any screening test uptake, this was highest in studies collected data after 2000 (OR 1.49, 95%CI 1.35, 1.65 and I^2 16.0%). 100.0% of the heterogeneity across all studies of the association between educational attainment and any screening test uptake can be explained by the year of data collection.

The meta-analysis of the association between income and colorectal cancer screening of cross-sectional studies are shown in Figure 3.3. Overall, those in the highest income groups were on average 32% (95% CI 18%, 49%) more likely to screen with any screening test than those in the lowest income group (with no heterogeneity). Screening uptake with endoscopy, FOBT and recommended screening tests was, 75% (95% CI 29%, 236%), 57% (95% CI 8%, 229%) and 42% (95% CI 16%, 75%), respectively, higher in the highest income group compared with the lowest. Here too, there was a moderate to high level of heterogeneity between studies, with I^2 estimates ranging from 63.7% to 98.4%. The subgroup and meta-regression analyses by age group, year of data collection or publication, country of participants recruitment, and race/ ethnicity are shown in Table 3.3. Studies conducted in minority group reported that those with the highest income level group had higher endoscopy (OR 2.72, 95% CI 1.75, 4.22 and I^2 0.0%) with no heterogeneity between studies. For endoscopy, studies published before and in 2008 (OR 2.50, 95% CI 1.42, 4.38 and I^2 57.8%) and after 2008 (OR 1.39, 95% CI 1.08, 1.78 and I^2 75.1%) demonstrated that those with the highest income level had higher screening uptake. Moreover, 50.5% and 46.3% of the heterogeneity of the studies of endoscopy were explained by year of publication and minority group, respectively.

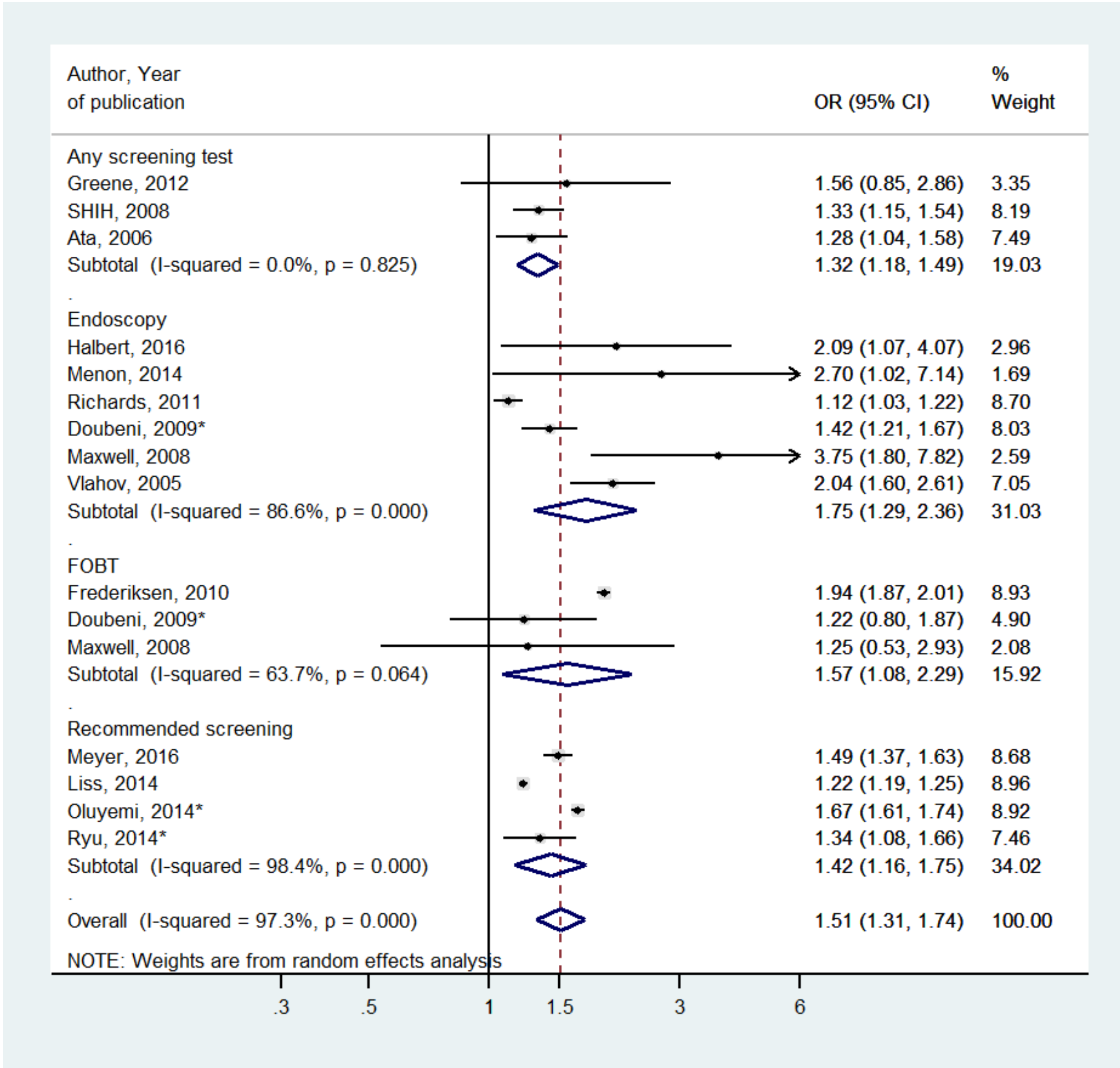


*An overall estimate of the study

Figure 3.2 Forest plots of the association between educational attainment and colorectal cancer screening modality (cross-sectional study)

Table 3.2 Meta-analysis (subgroup and Meta-regression) of the association between educational attainment and colorectal cancer screening uptake (cross-sectional study)

	N	OR	(95% CI)	I^2 (%)	Adjusted R^2
Educational attainment - any screening test	8	1.58	(1.33, 1.87)	77.9	
Age group					-
Aged 50 years old and older	8	1.58	(1.33, 1.87)	77.9	
Included aged younger than 50	0	-	-	-	
Year of data collection					100.0
Before and in 2000	4	1.79	(1.33, 2.40)	74.3	
After 2000	4	1.49	(1.35, 1.65)	16.0	
Country					0.0
The United States	7	1.57	(1.27, 1.93)	81.1	
Countries excluding the United States	1	1.52	(1.23, 1.86)	-	
Minority group					58.4
General population	6	1.71	(1.43, 2.03)	80.5	
Minority or high-risk group	2	0.94	(0.64, 1.40)	0.0	
Educational attainment - endoscopy	7	1.44	(1.16, 1.79)	73.5	
Age group					59.0
Aged 50 years old and older	6	1.32	(1.09, 1.58)	62.7	
Included aged younger than 50	1	2.75	(1.62, 4.66)	-	
Year of publication					0.0
Before and in 2008	2	1.72	(0.68, 4.38)	82.3	
After 2008	5	1.35	(1.10, 1.65)	69.8	
Country					-
The United States	7	1.44	(1.16, 1.79)	73.5	
Countries excluding the United States	0	-	-	-	
Minority group					0.0
General population	2	1.35	(0.91, 2.02)	88.5	
Minority or high-risk group	5	1.57	(1.08, 2.28)	66.9	
Educational attainment - FOBT	8	1.24	(1.04, 1.48)	82.7	
Age group					0.0
Aged 50 years old and older	6	1.24	(1.03, 1.49)	87.2	
Included aged younger than 50	2	1.28	(0.59, 2.78)	39.1	
Year of data collection					100.0
Before and in 2008	6	1.38	(1.33, 1.43)	0.0	
After 2008	2	1.07	(0.99, 1.15)	0.0	
Country					7.1
The United States	4	1.45	(1.06, 2.00)	12.7	
Countries excluding the United States	4	1.18	(0.96, 1.46)	91.8	
Minority group					0.0
General population	5	1.25	(1.03, 1.52)	89.6	
Minority or high-risk group	3	1.21	(0.79, 1.86)	0.0	
Educational attainment - recommended screening	5	1.53	(1.24, 1.88)	95.4	
Age group					40.2
Aged 50 years old and older	4	1.43	(1.15, 1.77)	96.2	
Included aged younger than 50	1	2.72	(1.65, 4.48)	-	
Year of data collection					61.3
Before and in 2008	2	2.03	(1.36, 3.04)	65.1	
After 2008	2	1.33	(1.14, 1.55)	76.5	
Country					40.2
The United States	4	1.43	(1.15, 1.77)	96.2	
Countries excluding the United States	1	2.72	(1.65, 4.48)	-	
Minority group					6.3
General population	4	1.63	(1.29, 2.07)	96.5	
Minority or high-risk group	1	1.15	(0.91, 1.45)	0.0	



*An overall estimate of the study

Figure 3.3 Forest plots of the association between income and colorectal cancer screening modality (cross-sectional study)

Table 3.3 Meta-analysis (subgroup and Meta-regression) of the association between income and colorectal cancer screening uptake (cross-sectional study)

	N	OR	(95% CI)	I^2 (%)	Adjusted R^2
Income - any screening test	3	1.32	(1.18, 1.49)	0.0	
Income - endoscopy	6	1.75	(1.29, 2.36)	86.6	
Age group					-
Aged 50 years old and older	6	1.75	(1.29, 2.36)	86.6	
Included aged younger than 50	0	-	-	-	
Year of publication					50.5
Before and in 2008	2	2.50	(1.42, 4.38)	57.8	
After 2008	4	1.39	(1.08, 1.78)	75.1	
Country					-
The United States	6	1.75	(1.29, 2.36)	86.6	
Countries excluding the United States	0	-	-	-	
Minority group					46.3
General population	3	1.45	(1.07, 1.98)	91.7	
Minority or high-risk group	3	2.72	(1.75, 4.22)	0.0	
Income - FOBT	3	1.57	(1.08, 2.29)	63.7	
Age group					-
Aged 50 years old and older	3	1.57	(1.08, 2.29)	63.7	
Included aged younger than 50	0	-	-	-	
Year of data collection					-
Before and in 2008	3	1.57	(1.08, 2.29)	63.7	
After 2008	0	-	-	-	
Country					100.0
The United States	2	1.23	(0.84, 1.80)	0.0	
Countries excluding the United States	1	1.94	(1.87, 2.01)	-	
Minority group					0.0
General population	2	1.62	(1.04, 2.52)	77.8	
Minority or high-risk group	1	1.25	(0.53, 2.93)	-	
Income - recommended screening	4	1.42	(1.16, 1.75)	98.4	
Age group					-
Aged 50 years old and older	4	1.42	(1.16, 1.75)	98.4	
Included aged younger than 50	0	-	-	-	
Year of data collection					43.0
Before and in 2008	1	1.67	(1.61, 1.74)	-	
After 2008	3	1.34	(1.15, 1.57)	89.6	
Country					-
The United States	4	1.42	(1.16, 1.75)	98.4	
Countries excluding the United States	0	-	-	-	
Minority group					0.0
General population	3	1.45	(1.15, 1.83)	98.9	
Minority or high-risk group	1	1.34	(1.08, 1.66)	-	

The association between composite indicators based on area of residence and colorectal cancer screening of three cross-sectional studies and a cohort study are shown in Figure 3.4. They suggested that people living in the least deprived areas were more likely to participate in colorectal cancer screening.

Funnel plots and Egger tests showed no evidence of publication bias for studies assessing the association between educational attainment and colorectal cancer screening uptake (Figure 3.5). For the association between income and colorectal cancer screening uptake, the possible publication bias was showed in the funnel plot and Egger's test of the association between income and endoscopy (Figure 3.6).

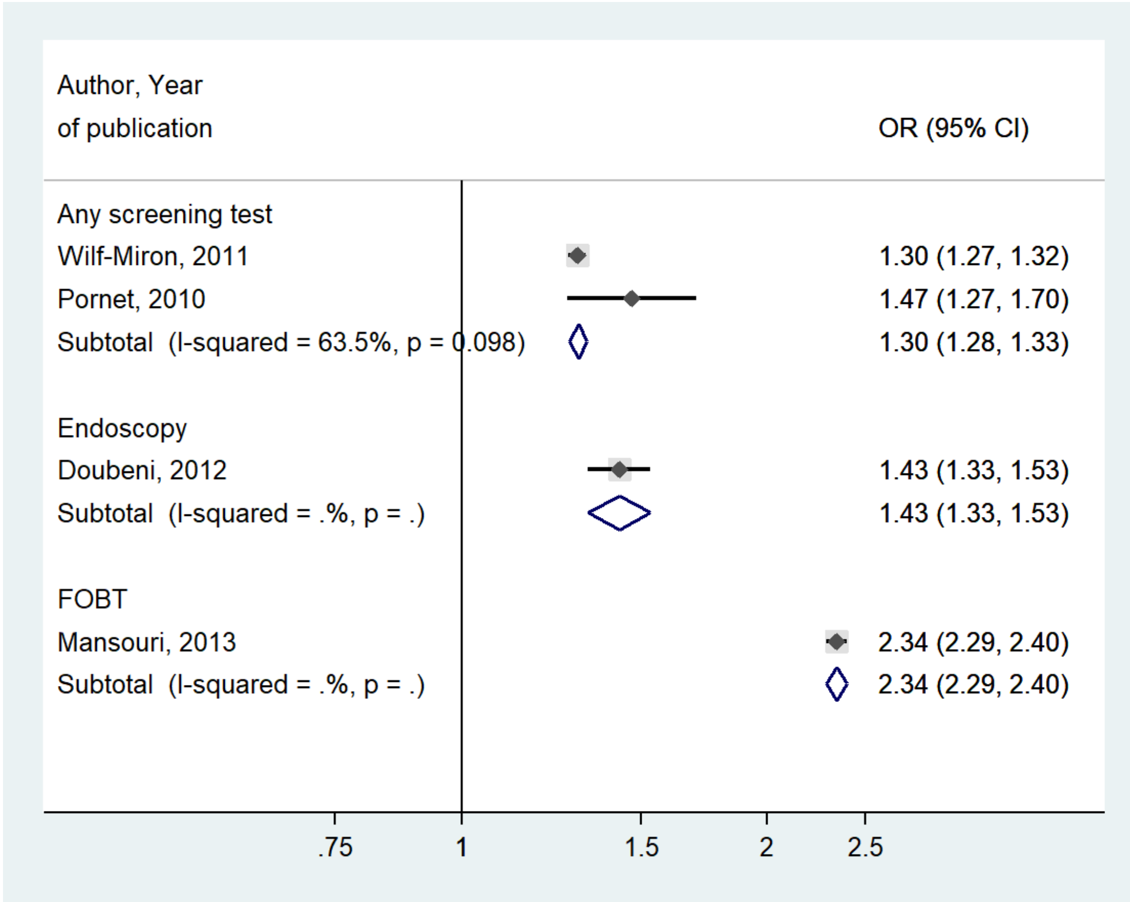


Figure 3.4 Association between composite indicators based on area of residence and colorectal cancer screening modality

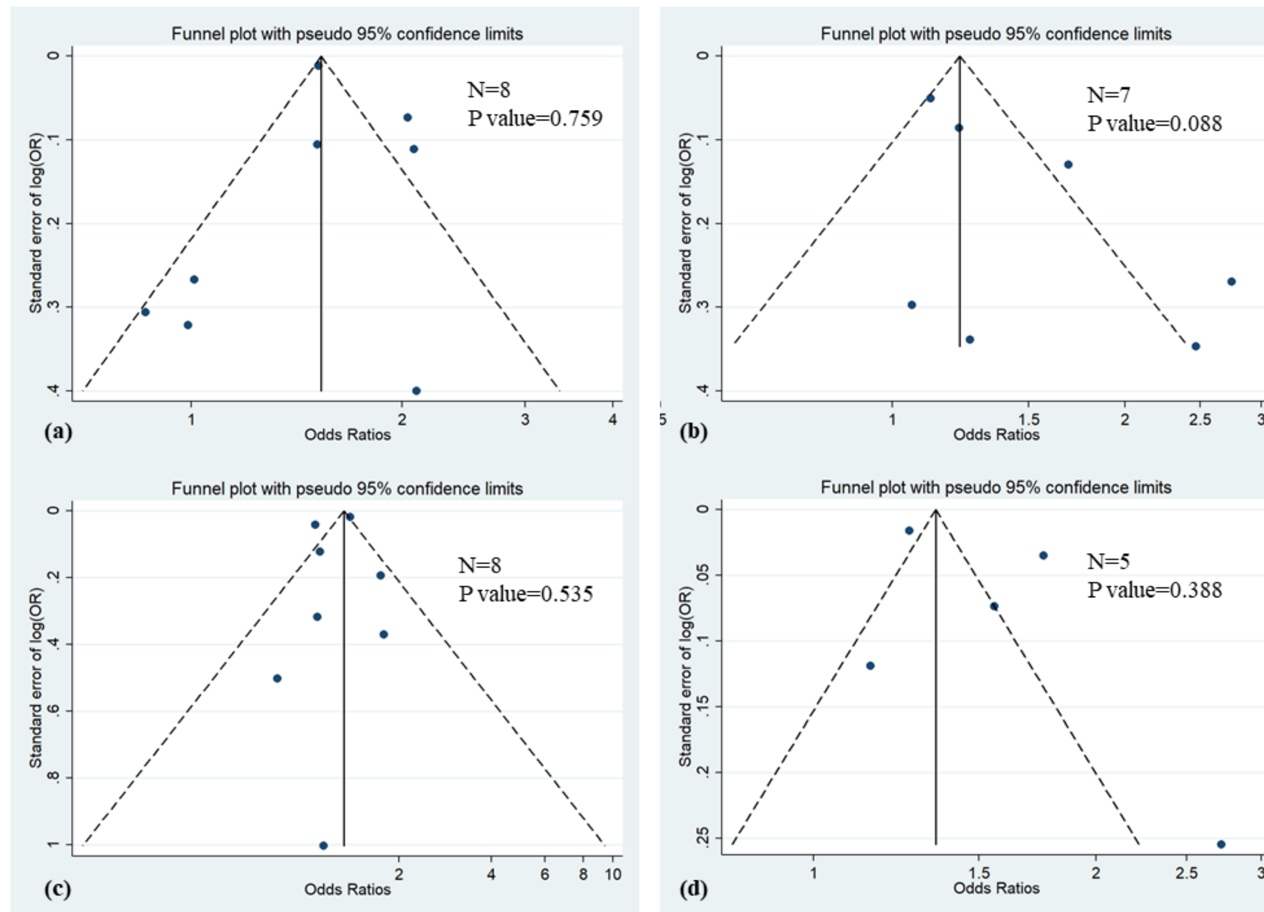


Figure 3.5 Funnel plots and Egger tests of the association between educational attainment and colorectal cancer screening modality: (a) any screening test, (b) endoscopy, (c) faecal occult blood test, and (d) recommended screening test.

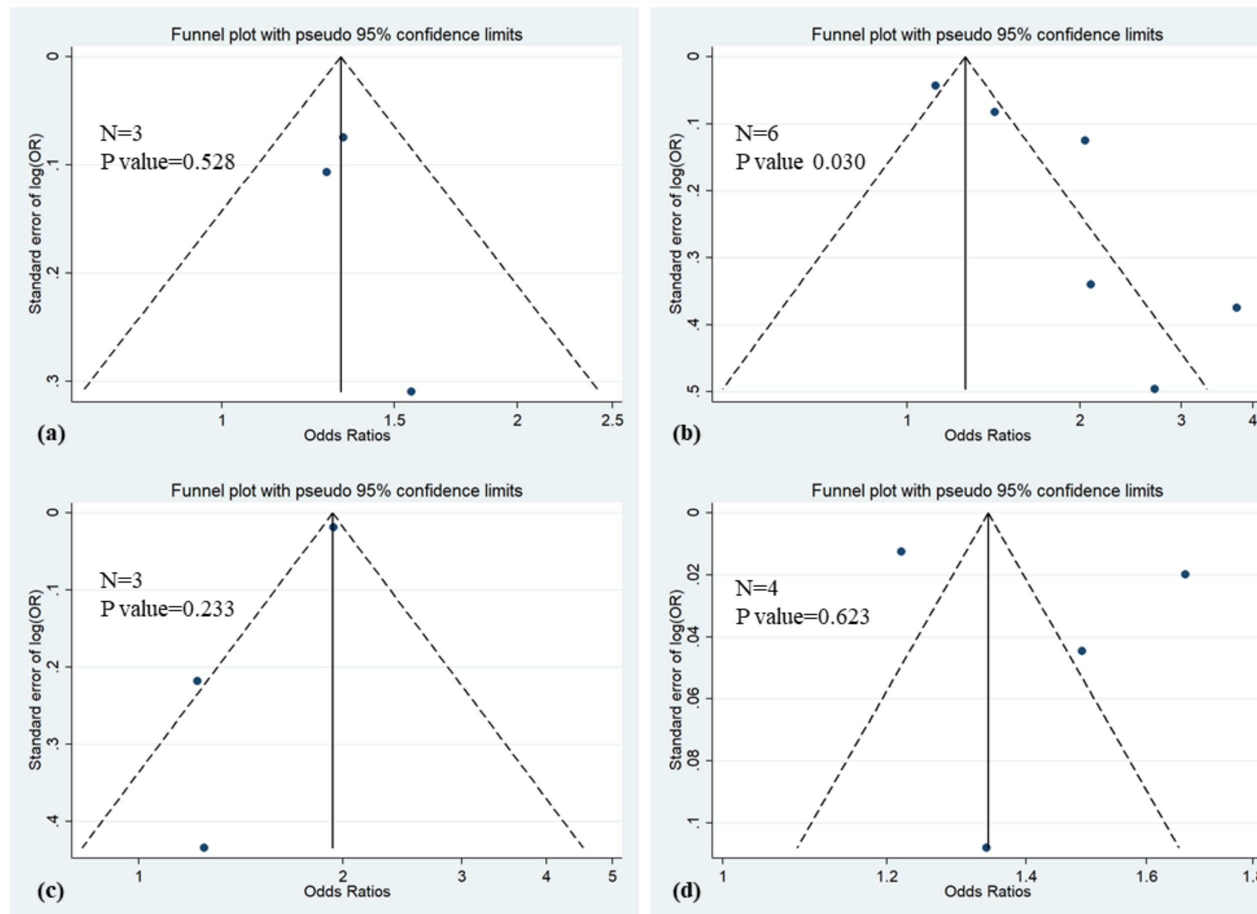


Figure 3.6 Funnel plots and Egger tests of the association between income and colorectal cancer screening modality: (a) any screening test, (b) endoscopy, (c) faecal occult blood test, and (d) recommended screening test.

3.4. Discussion

The main objective of this systematic review was to identify the degree to which socioeconomic status is associated with colorectal cancer screening participation for specific screening modalities. The included studies identified higher educational attainment and higher income as strong predictors of colorectal cancer screening uptake, regardless of the screening modality used or the country in which the studies were conducted. The overall estimate from meta-analysis of the association between socioeconomic status (educational attainment and income) and colorectal cancer screening uptake was added in the topic. Covariates that may explain the heterogeneity between the studies (such as year of data collection, country of study and race or minority groups) were highlighted in this review.

Five previous systematic reviews have investigated predictors of colorectal cancer screening participation(151-155). Three of the five previous reviews were limited to studies conducted in the United States where most screening is opportunistic(151-153). Their findings might therefore not be generalisable to other countries due to the unique characteristics of the United States healthcare system and access to screening. To my knowledge, this systematic review is the first to focus specifically on the relationship between socioeconomic status and colorectal cancer screening uptake and to consider studies from all countries.

Educational attainment and income were the most frequently used socioeconomic status indicators in the studies in this review. This is consistent with many previous health outcome studies(75) that have reported on educational attainment because it is regarded as a robust

proxy for employment prospects[78]. The positive association between educational attainment and health outcomes is thought to be mediated to a large extent by occupation and income. Those with higher educational attainment tend to have more stable jobs, higher incomes and better access to healthcare services, including screening[78, 81].

Another important mechanism linking education and health is health literacy[195, 199, 200]. The underlying rationale is that higher educational attainment might improve cognitive and emotional skills, which might lead to a greater ability to understand and act on health information such as recommendations to undergo regular colorectal cancer screening. Income affects health indirectly because it can determine health behaviours and access to healthcare services[162].

Composite indicators based on area of residence (such as the Townsend deprivation index[201]) are commonly used proxies for socioeconomic status[76]. In this review, I identified four studies using composite indicators and they suggested that people living in affluent areas were more likely to screen for colorectal cancer compared with those living in deprived areas. However, measures of association between the composite socioeconomic status indicators and individual health behaviours or status should be interpreted with caution due to a high risk of bias (i.e. ecological fallacy), which might lead to an underestimation of the association between socioeconomic status and screening participation[76, 162].

Overall, my results suggested that the social gradient of colorectal cancer screening is similar across healthcare systems (with different levels of publicly funded healthcare) and countries with organised and opportunistic approaches to colorectal cancer screening. This is consistent

with the findings of a recent review that investigated colorectal cancer screening participation for different socioeconomic groups in population-based colorectal cancer screening programs worldwide[202]. The authors reported that few of the current programs assess the impact of socioeconomic status on participation and that important disparities exist between socioeconomic groups within all the identified programs, which is consistent with the results of my analysis.

Based on a social determinants of health framework, intermediary determinants of health that are caused by socioeconomic position and affect people's health and wellbeing might be the keys to resolve health inequities. Many studies have shown that the association between socioeconomic status and colorectal cancer screening uptake is mediated mainly by accessibility to healthcare through, for example, the ability to purchase health insurance or to have the time and resources to attend regular doctor appointments. This is true in all countries, including those with universal health systems or organised screening programs. For example, in the United States a lack of health insurance represents one of the main barriers to endoscopy screening[181, 203-205]. But even among those eligible for Medicare insurance (i.e. people aged 65 years and older and therefore benefiting from free access to colorectal cancer services) lower screening participation rates have been reported for those with lower income and lower educational attainment[171]. Similarly, in the United Kingdom, where biennial colorectal cancer screening is offered free of charge to people aged 60–74 years, the uptake rate among program participants in the lowest socioeconomic quintile was 35% compared with 60% for those in the the highest socioeconomic quintile[159]. More generally, out-of-pocket costs have been identified as barriers to colorectal cancer screening

and access to healthcare[181]. There is evidence of a positive relationship between regular general practitioner visits and increased colorectal cancer screening uptake of FOBT[107, 203-207] and endoscopy[107, 203-206]. Patients who are at high risk of colorectal cancer or are aged 50 years and older might have a greater chance to get screening test recommendations if they have regular general practitioner visits.

Based on the Newcastle–Ottawa Scale assessment, the methodological quality of the included studies was moderate (average of 6.3 from maximum score of 10 for cross-sectional studies). Most of the included studies received the maximum score for comparability because they used multivariate models to adjust their analysis for potential confounding factors. Most studies were based on self-reported outcomes and therefore failed to obtain the maximum score in terms of measurement. The studies' overall quality score depended mainly on the selection factor, which required information on the representativeness, size of the study, non-respondents and ascertainment of the exposure. Generally, the Newcastle–Ottawa Scale is quite practical, but it does not provide a standard category (e.g. good, fair or poor) of quality for each study[86].

Because of the high heterogeneity between the studies, the subgroup analyses and meta-regression played major roles in this study. In these analyses, I found that country of study, year of data collection or publication and studies of minority groups were the key factors for explaining the heterogeneity of the association between socioeconomic status and colorectal cancer screening uptake. For example, the United States as the country of study can explain the heterogeneity between the studies of several associations between socioeconomic status and screening modality. This reflects differences between the United States and other

countries. Healthcare systems and colorectal cancer screening programs are good examples of these differences. Most European countries, Canada and Australia have universal healthcare systems, while the United States uses private health insurance in general and Medicare for the elderly. Moreover, most European countries, Canada and Australia have organised screening programs based on FOBT. In contrast, the United States has opportunistic colorectal cancer screening that relies on guidelines that recommend colonoscopy every ten years, sigmoidoscopy every five years or FOBT annually(46). Studies conducted in the United States and based on cohort studies(168, 175, 188) or Medicare records(171) reported moderate to high screening uptake rate, while the percentage of screening uptake in other countries based on national bowel cancer screening programs(190, 192-194, 196) were low to moderate. These create large socioeconomic disparities in colorectal cancer screening uptake in the United States compared with other countries.

There was variety among studies conducted in the United States. The subgroup analysis and meta-regression found that minority groups and year of data collection were the other possible covariates to explain the heterogeneity between studies. Minority groups such as migrants, Latinos and African-Americans have different risks of developing colorectal cancer compared with Caucasians. The accessibility to healthcare of minority groups is limited compared with Caucasians as seen through the lower colorectal cancer screening uptake in minority groups(172, 176, 178, 180, 188). Studies have reported, however, that these differences decrease substantially or sometimes disappear when adjusting for educational attainment and income level(208). With respect to the year of data collection, the colorectal cancer screening clinical guidelines of the US Preventive Services Task Force recommendation were launched

in 2008[209]. These were more evidence-based compared with the previous guidelines. In addition, the Patient Protection and Affordable Care Act, which passed the US Congress in 2010, likely reduced the disparities of healthcare accessibility for most Americans, especially for disadvantaged groups[210]. These important health-related events in the United States might narrow the gap of socioeconomic disparities in colorectal cancer screening uptake in the United States by generally increasing the screening uptake for all Americans.

Between-study heterogeneity was driven in part by data source differences. Some studies used data specifically collected to answer research questions on colorectal cancer screening. These were usually based on small surveys but have substantial sets of covariates. Other studies used administrative databases – such as the United States Medicare records and the United States National Health Insurance Survey data – or combined data from multiple sources, which allowed for larger studies but provided less granularity. Nevertheless, socioeconomic disparities on health and healthcare system are quite complicated and beyond the scope of this study. Some heterogeneity cannot be explained in this study.

A main limitation of this systematic review is the fact that most of the studies were cross-sectional analyses. There is only one cohort study in this review. The cross-sectional study has an issue on temporal relationship between the exposure and the outcome. So, doing meta-analysis on ORs from cross-sectional study might introduce serious bias to the analysis. However, my focus is the socioeconomic disparities on colorectal cancer screening uptake, which is unlikely to be examined in randomised controlled trials. Therefore, the results and pooled estimates were therefore exposed to the effect of potential confounders.

Colorectal cancer screening participation is a complex health behaviour that is affected by multiple determinants. In this study I provided estimates of the association between specific screening modalities and socioeconomic status indicators. My meta-analyses support findings previously reported in narrative reviews and the grey literature and highlight the fact that deprived populations are less likely to screen and are therefore less likely to access the health benefits of regular colorectal cancer screening. This result was consistent across a variety of healthcare and screening organisation settings. To mitigate this risk and maximise the effectiveness of current and future colorectal cancer screening initiatives, it is important to have a precise assessment of the social gradient observed in the population in terms of screening participation. Additionally, further study should confirm my findings by recruiting more cohort and case-control studies. More effective strategies to reach out to people in low socioeconomic groups are needed to reduce the high burden of colorectal cancer experienced by these vulnerable populations.

Chapter 4. Socioeconomic Status and Risk of Colorectal Cancer: A Systematic Review and Meta-analysis

4.1. Introduction

Colorectal cancer risk might differ by socioeconomic status given screening for the disease as well as risk factors might depend on factors such as income, educational attainment and access to healthcare. This sociodemographic gradient in colorectal cancer risk is seen worldwide. However, reports on the magnitude of this association and even the direction of the association vary geographically and may thus lead to misguided or inconsistent prevention and control measures.

There have been four previous reviews[71, 72, 152, 211] on the association between socioeconomic status and risk of colorectal cancer. The earliest review[211], using data from industrialized countries, found that higher socioeconomic status groups likely had greater risk of colon cancer; there was an inconsistent association between socioeconomic status and risk of rectal cancer. The second review[152], based on the United States' studies only and using the United States colorectal cancer disparities grid, concluded that the lower socioeconomic status group had lower screening uptake, higher cancer incidence and greater mortality rates. The third and fourth reviews[71, 72] assessed 19 studies and 21 studies worldwide respectively and

demonstrated contradictory results between North America and other continents. In the United States and Canada, lower social class was associated with greater risk of colon and rectal cancers, while most of the European studies showed that lower socioeconomic status groups had lower risk of these cancers. Possible reasons for this geographic difference include differences in lifestyle (risk) factors[71, 72], colorectal cancer screening uptake[71, 72] and difference in access to healthcare system[72]. However, these reviews did not perform further analysis to test these hypotheses. Moreover, none of the reviews performed meta-analysis.

The aims of this study were: to investigate the association between socioeconomic status, defined by educational attainment, income, and composite socioeconomic status indicators based on area of residence, and risk of colon, rectal and colorectal cancers; and to explore the possible reasons for any heterogeneity of these associations by using subgroup analysis and meta-regression techniques.

4.2. Methods

4.2.1. Search strategy and study selection

I searched Embase, MEDLINE, PsycINFO, and Cochrance library databases, up to January 2018, to identify observational studies investigating the association between socioeconomic status and risk of colon, rectal, and colorectal cancers. The following combinations of search terms were used: colorectal neoplasms (MeSH) or colorectal cancer$.mp. or CRC.mp. or colorectal neoplasm$.mp. or colon cancer$.mp. or colon neoplasm$.mp. or colonic neoplasm$.mp. or colonic cancer$.mp. or rectal neoplasm$.mp. or rectal cancer$.mp. or

bowel cancer$.mp. and risk (MeSH) or risk$.mp. or incidence (MeSH) or incidence$.mp. and socioeconomic factors (MeSH) or education (MeSH) or ethnic groups (MeSH) or health status disparities (MeSH) or social determinants of health (MeSH) or social determinants$.mp. or socioeconomic status.mp. The search was limited to peer-reviewed articles published in English. Additionally, I hand searched all studies referenced by the four previous reviews of the association between socioeconomic status and colorectal cancer risk[71, 72, 152, 211].

All observational study designs were eligible for inclusion the systematic review. However, only cohort and case-control studies were considered for meta-analyses. To be included, studies had to report a measure of association between socioeconomic status (educational attainment, income or composite socioeconomic status indicators based on area of residence) and colon, rectal or colorectal cancer risk based on multivariate models along with 95% CI. Studies providing the measures of association on a continuous scale of socioeconomic status were excluded from the review.

In this analysis, I defined income including individual income, family income and poverty level. Composite socioeconomic status indicator based on area of residence is an indicator that combines a variety of neighbourhood-level variables into a single quantity[114, 162].

4.2.2. Data extraction and quality assessment

The following information was extracted for all the included studies: author's name; year of publication; country of study; study design; year of data collection; source of data; participants' characteristics (sex, age group and race/ethnicity); definition of socioeconomic

status; measure of association with the corresponding 95% CI; and factors adjusted for in the multivariable model. The references of the included studies were checked for articles fulfilling this review's inclusion criteria.

Quality assessment of each of the study was evaluated with ROBINS-I[88]. This tool consists of seven bias domains: confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported results. The overall risk of bias was categorised as:

- low risk of bias (the study is comparable to a well-performed randomised controlled trial) which is at low risk of bias for all domains;
- moderate risk of bias (the study appears to provide sound evidence for a non-randomized study but cannot be considered comparable to a well-performed randomised controlled trial) which is at low or moderate risk bias for all domains;
- serious risk of bias (the study has some important problems) which is at serious risk of bias in at least one domain, but not at critical risk of bias in any domain;
- critical risk of bias (the study is too problematic to provide any useful evidence and should not be included in any synthesis) which is at critical risk of bias in at least one domain.

4.2.3. Data synthesis and statistical analysis

In order to be coherent between the studies, only a measure of association between the lowest and the highest level of socioeconomic status was included in the meta-analyses. The highest level of educational attainment, income or composite socioeconomic status indicator based on area of residence was set as the reference category, i.e. an OR of less than one is indicative of lower socioeconomic status group having a lower risk of colorectal cancer, and an OR of greater than one indicative of lower socioeconomic status group having a greater risk of colorectal cancer. For studies providing several measures of association an overall estimate was calculated for each study using meta-analyses. Only one measure of association, from each individual study, was included in the meta-analyses. The meta-analyses were conducted separately by socioeconomic status indicator (educational attainment, income, and composite indicator based on area of residence) and cancer site (colon, rectum and colorectum) so as to calculate the site-specific pooled estimates. The measures of association from cross-sectional studies were excluded from the meta-analyses. A random effect model was used to produce pooled estimates from the fully adjusted ORs and CIs of the individual studies. Between-study heterogeneity was assessed using the Cochrane Q ($\chi 2$ test) and I^2 statistics. Funnel plot asymmetry and Egger tests were assessed to determine evidence for publication bias. Subgroup analyses were conducted including sex, continent of studies and study design. Sensitivity analyses of meta-regression were performed to assess the covariates effect on the pooled result estimates and accompanying heterogeneity.

4.3. Results

4.3.1. Study selection

I excluded: 1,780 non-relevant studies, 12 studies which used only occupation as a measure of socioeconomic status, 11 studies which did not provide any measure of association and 95% CI, six studies which used relative index of inequality or standardised incidence ratio, five studies that did not present adjusted measure of associations, three reviews, three prevalence studies, two studies with measure of association of socioeconomic status on a continuous scale, an ecological study, and a study using the same study population as another study. There were 34 studies included in this review (Figure 4.1).

4.3.2. Study characteristics

Characteristics of 34 studies are presented in Table 4.1. Briefly, 15 studies were conducted in America (the United States[80, 141, 212-221], Canada[218, 222, 223] and Puerto Rico[224]), 16 in Europe (Italy[225-229], Netherland[230, 231], Ireland[232, 233], Scotland[234, 235], Denmark[236], Norway[237], Germany[238], Spain[239] and a study in multiple Europeans countries[240]), and three studies were conducted in the other continents (Korea[241], Japan[242] and Australia[243]). Year of publication ranged from 1992 to 2018. Year at which collected socioeconomic data referred to, ranged from 1945[221] to 2012. There were 15 cohort[80, 141, 213, 214, 216, 217, 219, 221, 226, 230, 231, 236, 237, 240, 242], 5 case-control[223, 225, 227-229] and 14 cross-sectional[212, 215, 218, 220, 222, 224, 232-235, 238, 239, 241, 243] studies. Nineteen (55.9% studies conducted the analyses for cancer in a specific site of colorectum[80, 141, 212, 215, 218-220, 222, 223, 225-227, 229, 236, 237, 240-243] and 14 (41.2%) studies did not specify the site within the colorectum [213, 214, 216, 217, 221, 224, 228, 230, 232-

[235, 238, 239]. Fifteen studies used educational attainment[141, 212, 214, 219, 223, 225-231, 236, 237, 240] as the socioeconimic variable, 15 used composite socioeconomic status indicator based on area of residence[80, 141, 213, 216, 220, 221, 224, 232-235, 238, 239, 242, 243], and seven studies used income[212, 214, 215, 217, 218, 222, 241]. There were five the United States' studies which included subgroup analysis on racial groups[212, 213, 215, 217, 220]. Details of the association between socioeconomic status and colorectal cancer risk are seen in the Appendix B (educational attainment (Appendix B table 1–3), income (Appendix B table 4–6) and composite indicator based on area of residence (Appendix B table 7–9)).

Results for the quality assessment of individual studies are presented in Table 4.1 and Appendix B table 10. Briefly, only four articles[141, 213, 219, 231] had moderate risk of bias. The others (30/34) had serious risk of bias. Risk of bias due to confounding domain played a major role on the overall risk of bias. Of the 34 articles, five articles[80, 141, 215, 228, 242] were unclear about missing data. No studies received critical risk of bias for any ROBINS-I domain.

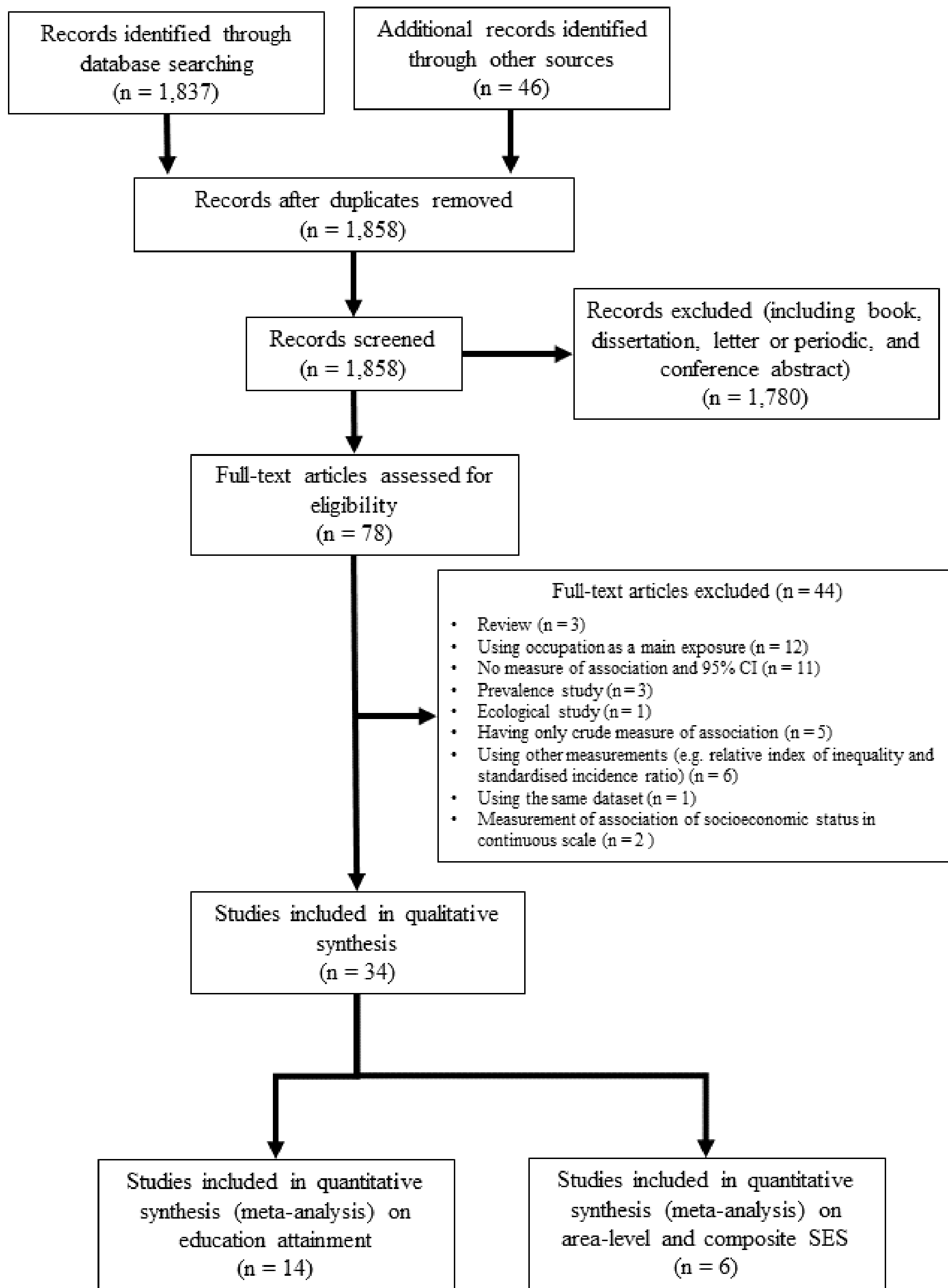


Figure 4.1 Flow chart of study selection process

Table 4.1 Characteristics of 34 included studies

Author, year	**Country of participants recruitment**	**Source of data**	**Reference year**	**Study design**	**Target age group**	**Sex-specific analyses**	**Race/Ethnicity#**	**Cancer sites (outcome)**	**Socioeconomic status indicators (exposure)**	**Risk of bias (ROBINS-I)**
Tweed, 2018*[235]	Scotland	West of Scotland Cancer Surveillance Unit, which holds regional data from the Scottish Cancer Registry	2001–2012	Cross-sectional study	Non-specific	Male and female	Non-specific	CRC	Scottish index of multiple deprivation	Serious
Canchola, 2017[213]	United States	Multiethnic Cohort Study, Hawaii and California	1993–2010	Cohort study	Non-specific	Male and female	African Americans, Japanese Americans, Latinos, Caucasians	CRC	Neighborhood SES	Moderate
Stroup, 2017[221]	United States	Utah Population Database and Utah Cancer Registry	1945–2009	Cohort study	Non-specific	Combined	Non-specific	CRC	Neighborhood SES, or birth certificate census tract SES	Serious
Liu, 2016[217]	United States	Texas Cancer Registry	1995–2011	Cohort study	Non-specific	Combined	Non-Hispanic Caucasians, Non-Hispanic Blacks, Hispanics, Asian/ Pacific Islander/ American Indians/ unspecific	CRC	Median household income	Serious
Hastert, 2015[216]	United States	The VITamins And Lifestyle study	2000–2010	Cohort study	50-76	Combined, male and female	Non-specific	CRC	Area-level SES	Serious
Garcia-Gil, 2014*[239]	Spain	The Information System for the Development of Research in Primary Care	2009–2012	Cross-sectional study	Non-specific	Combined, male and female	Non-specific	CRC	The ecological MEDEA index	Serious
Miki, 2014[242]	Japan	The Japan Public Health Center-based Prospective Study Cohorts I and II	1990–2009	Cohort study	40-69	Male and female	Japanese	CRC*, colon and rectum	The Japanese deprivation index	Serious

Author, year	Country of participants recruitment	Source of data	Reference year	Study design	Target age group	Sex-specific analyses	Race/Ethnicity#	Cancer sites (outcome)	Socioeconomic status indicators (exposure)	Risk of bias (ROBINS-I)
Steinbrecher, 2012*[220]	United States	The California Cancer Registry	1998–2002	Cross-sectional study	Non-specific	Combined	Non-Hispanic Caucasians, African American, Hispanics, Asian/ Pacific Islander	CRC, left colon, right colon and rectum	SES quintile	Serious
Leufkens, 2012[240]	European countries	The European Prospective Investigation into Cancer and Nutrition study	1991–2006	Cohort study	Non-specific	Combined	Non-specific	CRC*, colon and rectum	Education	Serious
Doubeni, 2012[141]	United States	The ongoing prospective NIH– AARP Diet and Health Study	1995–2006	Cohort study	50–75	Combined	Non-specific	CRC*, right colon, left colon and rectum	Education, Neighbor deprivation	Moderate
Kim, 2012*[241]	Korea	The 2009 Korean National Health Insurance cancer registration	2009	Cross-sectional study	Non-specific	Male and female	Koreans	Colon and rectum	Income class	Serious
Kuznetsov, 2012*[238]	Germany	The Population based Cancer Registry of Bavaria	2003–2006	Cross-sectional study	Non-specific	Combined, male and female	Non-specific	CRC	Bavarian Index of Multiple Deprivation	Serious
Torres-Cintron, 2012*[224]	Puerto Rico	The Puerto Rico Central Cancer Registry	1995–1999, 2000–2004	Cross-sectional study	Non-specific	Male and female	Non-specific	CRC	Socioeconomic position index	Serious
Donnelly, 2011*[232]	North Ireland	The Northern Ireland Cancer Registry	1995–2007	Cross-sectional study	Non-specific	Combined	Non-specific	CRC	The Multiple deprivation measure	Serious
Oilphant, 2011*[234]	Scotland	The Scottish Cancer Registry of the West of Scotland	1999–2001, 2002–2004, 2005–2007	Cross-sectional study	Non-specific	Male and female	Non-specific	CRC	Scottish Index of Multiple deprivation	Serious

Author, year	Country of participants recruitment	Source of data	Reference year	Study design	Target age group	Sex-specific analyses	Race/Ethnicity[#]	Cancer sites (outcome)	Socioeconomic status indicators (exposure)	Risk of bias (ROBINS-I)
Kim, 2010[80]	United States	The Nurses' Health Study	1986–2006	Cohort study	30–55	Female	Non-specific	Colon and rectum	Neighborhood socioeconomic score	Serious
Clegg, 2009[214]	United States	The SEER and the United States representative National Longitudinal Mortality Study	1973–2001	Cohort study	≥25	Combined	Non-specific	CRC	Education and income	Serious
Spadea, 2009[226]	Italy	The Turin Longitudinal Study	1985–1999	Cohort study	30-74	Male and female	Non-specific	Colon and rectum	Education	Serious
de Kok, 2008[230]	Netherland	The prospective GLOBE study	1991–2005	Cohort study	15–74	Combined	Non-specific	CRC	Education	Serious
Goy, 2008[223]	Canada	A population-based case-control study from Southern Ontario	1992–1994	Case-control study	25–65	Combined	Non-specific	Colon and rectum	Education	Serious
Egeberg, 2008[236]	Denmark	3.22 million Danish residents born between 1925 and 1973 without a previous cancer and who entered the cohort at age 30	1994–2003	Cohort study	≥30	Male and female	Non-specific	Colon and rectum	Education	Serious
Mouw, 2008[219]	United States	The NIH– AARP Diet and Health Study	1995–1996	Cohort study	50–71	Male and female	Non-specific	Colon and rectum	Education	Moderate
Braaten, 2005[237]	Norway	The Norwegian Women and Cancer Study	1991–2001	Cohort study	30–69	Female	Non-specific	Colon and rectum	Education	Serious
Pisa, 2000[225]	Italy	A multicenter hospital-based case-control study on cancer of the colon and rectum	1992–1996	Case-control study	Non-specific	Combined*, male and female	Non-specific	Colon and rectum	Education	Serious
Mackillop, 2000*[218]	United States, Canada	The populations of Ontario and the SEER areas of the United States	1990–1991	Cross-sectional study	Non-specific	Male and female	Non-specific	Colon and rectum	Median household income	Serious
Tavani, 1999[227]	Italy	Two case-control studies of colorectal cancer	1985–1996	Case-control study	Non-specific	Combined*, male and female	Non-specific	Colon and rectum	Education	Serious

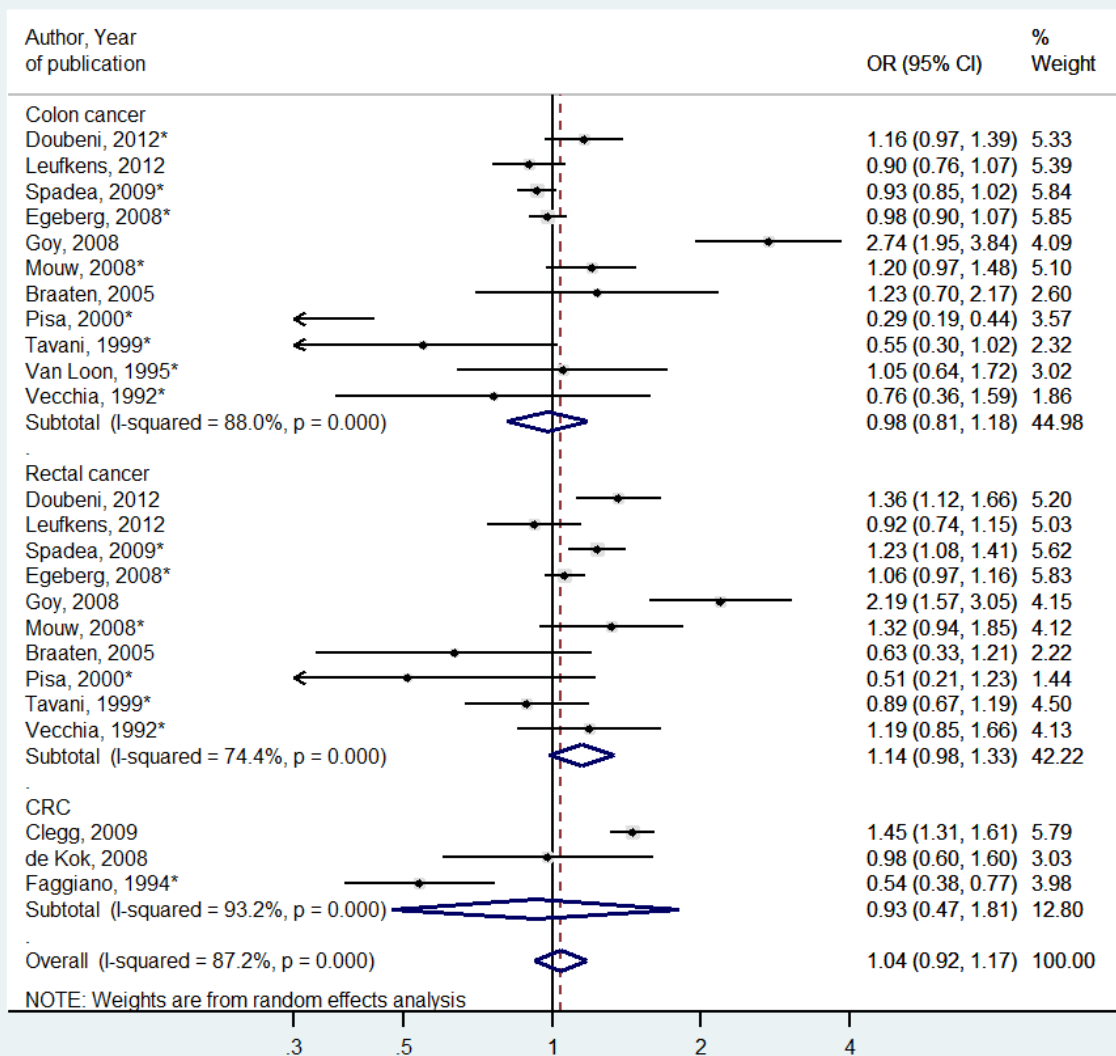
Author, year	Country of participants recruitment	Source of data	Reference year	Study design	Target age group	Sex-specific analyses	Race/Ethnicity[#]	Cancer sites (outcome)	Socioeconomic status indicators (exposure)	Risk of bias (ROBINS-I)
Gorey, 1998*[222]	Canada	The Ontario Cancer Registry	1986–1993	Cross-sectional study	≥25	Male and female	Non-specific	Colon and rectum	Income	Serious
Smith, 1996*[243]	Australia	The New South Wales Central Cancer Registry	1987–1991	Cross-sectional study	Non-specific	Male and female	Non-specific	Colon and rectum	Index of Relative Socioeconomic Disadvantage	Serious
Kee, 1996*[233]	Ireland	The Northern Ireland colorectal cancer register	1990–1991	Cross-sectional study	Non-specific	Combined	Non-specific	CRC	Townsend deprivation score	Serious
Van Loon, 1995[231]	Netherland	The Netherlands Cohort Study	1986–1989	Cohort study	Non-specific	Male and female	Non-specific	Colon	Education	Moderate
Gorey, 1995*[215]	United States	The New York State cancer registry	1979–1986	Cross-sectional study	Non-specific	Male and female	Caucasians and African Americans	Colon and rectum	Census tract poverty status	Serious
Faggiano, 1994[228]	Italy	Record linkage between the cancer registry (Registro Tumori Piemonte) and the census data of the Turin population (Studio Longitudinale Torinese)	1981–1989	Case-control study	Non-specific	Male and female	Non-specific	CRC	Education	Serious
Vecchia, 1992[229]	Italy	An integrated series of hospital-based case-control studies	1983–1990	Case-control study	<75	Combined*, male and female	Non-specific	Colon and rectum	Education	Serious
Baquet, 1991*[212]	United States	The San Francisco-Oakland, Detroit, and Atlanta cancer registries of the SEER	1978–1982	Cross-sectional study	≥25	Combined	Caucasians and African Americans	Colon and rectum	Education and median annual family income	Serious

[#]Race/ethnicity categories as reported in the publication

*were not included in the meta-analyses

4.3.3. Meta-analysis and publication bias

The individual ORs and pooled estimates (95% CI) of the association between educational attainment and risk of colorectal cancer from cohort and case-control studies is shown in Figure 4.2. Overall, there was no evidence of association between educational attainment and risk of colorectal cancer (OR 1.04, 95% CI 0.92, 1.17 and I^2 87.2%). The subgroup and meta-regression analyses by sex, continent in which study was conducted, and study design are shown in Table 4.2. Of studies conducted in North America, people with the lowest level of educational attainment had higher risk of any colorectal (OR 1.50, 95% CI 1.26, 1.79 and I^2 79.2%) and rectal (OR 1.56, 95%CI 1.16, 2.09 and I^2 69.2%) cancers. While studies conducted outside North America reported that those with the lowest level of educational attainment had lower risk of any colorectal (OR 0.88, 95% CI 0.78, 0.99 and I^2 77.6%) and colon (OR 0.81, 95% CI 0.68, 0.98 and I^2 81.1%) cancers. For risk of rectal cancer, this was highest in studies which included both sexes (OR 1.17, 95%CI 1.01, 1.36 and I^2 75.0%). For risk of any colorectal cancer, cohort studies (OR 1.10, 95% CI 1.00, 1.21 and I^2 79.3%) reported that those with the lowest level of educational attainment had higher risk of colorectal cancer. There was a high degree of heterogeneity across studies ($I^2 = 87.2\%$). This high heterogeneity was evident for colon ($I^2 = 88.0\%$), rectal ($I^2 = 74.4\%$) and colorectal ($I^2 = 93.2\%$) cancers. Heterogeneity across the studies of the association between educational attainment and risk of colorectal cancer risk can be explained by the continent in which the studies were conducted (32.0%–65.5%).



*An overall estimate of the study

Figure 4.2 Overall estimates of the association between educational attainment and risk of colorectal cancer (from cohort and case-control studies)

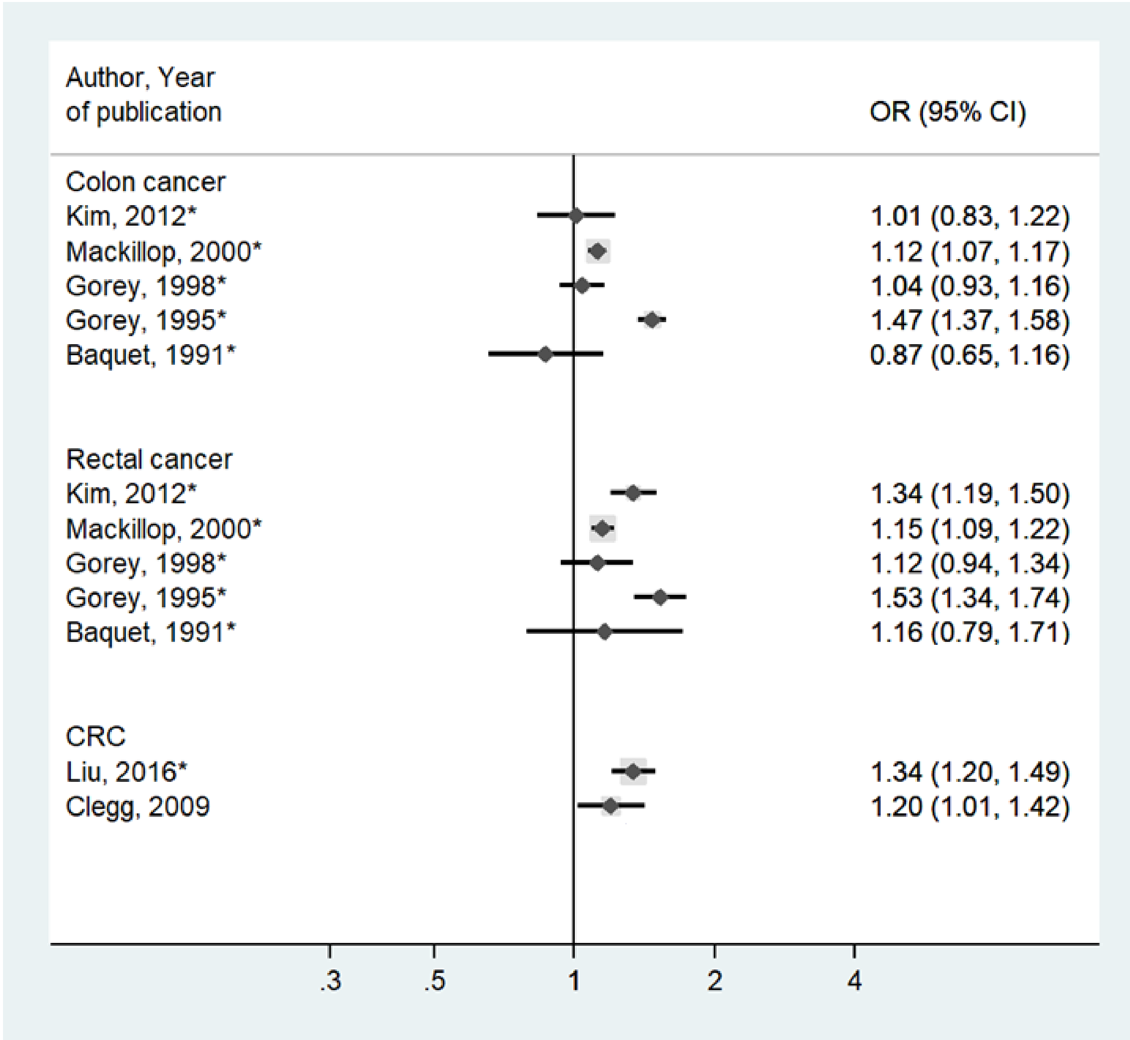
Table 4.2 Meta-analysis (subgroup and Meta-regression) of the association between educational attainment and colorectal cancer risk (from cohort and case-control studies)

	N	OR	(95% CI)	I^2 (%)	Adjusted R^2
Educational attainment - any colorectal cancer	24	1.04	(0.92, 1.18)	87.2	
Sex					0.0
Combined both sexes	21	1.05	(0.93, 1.19)	88.1	
Females	2	0.90	(0.47, 1.73)	57.0	
Males	0	-	-	-	
Continents					46.3
Europe & others	17	0.88	(0.78, 0.99)	77.6	
North America	7	1.50	(1.26, 1.79)	79.2	
Study design					0.0
Cohort study	15	1.10	(1.00, 1.21)	79.3	
Case-control	9	0.86	(0.52, 1.43)	92.8	
Educational attainment - colon cancer	11	0.98	(0.81, 1.18)	88.0	
Sex					0.0
Combined both sexes	10	0.96	(0.79, 1.17)	89.1	
Females	1	1.24	(0.70, 2.17)	-	
Males	0	-	-	-	
Continents					32.0
Europe & others	8	0.81	(0.68, 0.98)	81.1	
North America	3	1.53	(0.99, 2.35)	90.3	
Study design					0.0
Cohort study	7	1.00	(0.93, 1.09)	38.9	
Case-control	4	0.76	(0.23, 2.55)	95.9	
Educational attainment - rectal cancer	10	1.14	(0.98, 1.33)	74.4	
Sex					14.1
Combined both sexes	9	1.17	(1.01, 1.36)	75.0	
Females	1	0.63	(0.33, 1.21)	-	
Males	0	-	-	-	
Continents					65.5
Europe & others	7	1.03	(0.90, 1.17)	54.6	
North America	3	1.56	(1.16, 2.09)	69.2	
Study design					0.0
Cohort study	6	1.13	(0.98, 1.29)	63.9	
Case-control	4	1.13	(0.68, 1.87)	85.3	
Educational attainment - colorectal cancer	3	0.93	(0.47, 1.81)	93.2	
Sex					-
Combined both sexes	3	0.93	(0.47, 1.81)	93.2	
Females	0	-	-	-	
Males	0	-	-	-	
Continents					45.7
Europe & others	2	0.71	(0.40, 1.27)	73.2	
North America	1	1.45	(1.31, 1.61)	-	
Study design					81.6
Cohort study	2	1.29	(0.90, 1.83)	57.4	
Case-control	1	0.54	(0.38, 0.77)	-	

Meta-analysis on the association between income level and risk of colorectal cancer was not conducted because there were five cross-sectional studies out of seven included studies. The association between income level and colorectal cancer categorised by cancer site is presented graphically in Figure 4.3 but the pooled estimate is not provided. Most of the studies showed that those with the lowest income level had higher risk of colorectal cancer compared to those with the highest income level.

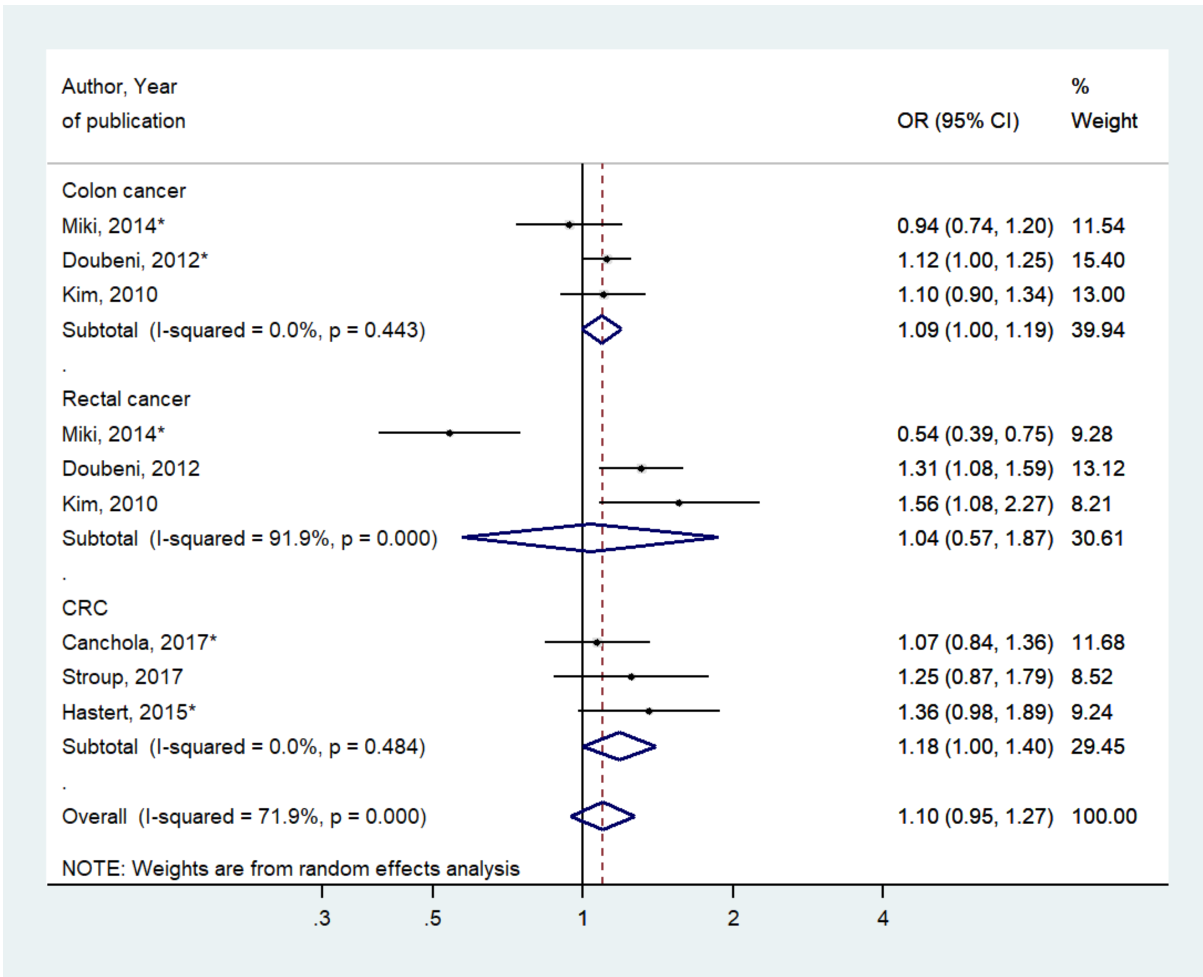
The individual ORs and pooled estimates (95% CI) of the association between composite socioeconomic status indicator based on area of residence and risk of colorectal cancer is shown in Figure 4.4. Overall, there was no evidence of association between the composite socioeconomic status indicator and risk of colorectal cancer (OR 1.10, 95% CI 0.95, 1.27 and I^2 71.9%). The subgroup and meta-regression analyses are reported in Table 4.3. People who lived in the lowest socioeconomic status area had greater risk of colon (OR 1.09, 95% CI 1.00, 1.19 and I^2 0.0%) and colorectal cancer (OR 1.18, 95% CI 1.00, 1.40 and I^2 0.0%) compared to those who lived in the highest socioeconomic status area. For the studies conducted in North America, people who lived in the most deprived area had higher risk of any colorectal (OR 1.17, 95% CI 1.09, 1.27 and I^2 1.4%) and rectal (OR 1.36, 95% CI 1.15, 1.62 and I^2 0.0%) cancers compared to those who lived in the least deprived areas. Most of the heterogeneity between the studies on any colorectal cancer (adjusted R^2 78.5%) and all the heterogeneity of the studies on rectal cancer (adjusted R^2 100.0%) can be explained by the continent in which the studies were conducted (Table 4.3).

Funnel plots and Egger's test indicated no evidence of publication bias for studies of educational attainment (Figure 4.5) and studies of composite socioeconomic status indicators based on area of residence (Figure 4.6).



*An overall estimate of the study

Figure 4.3 Association between income level and risk of colorectal cancer (from all observational studies)



*An overall estimate of the study

Figure 4.4 Overall estimates of the association between composite indicators based on area of residence and risk of colorectal cancer (from cohort and case-control studies)

Table 4.3 Meta-analysis (subgroup and Meta-regression) of the association between composite indicators based on area of residence and colorectal cancer risk (from cohort and case-control studies)

	N	OR	(95% CI)	I^2 (%)	Adjusted R^2
Area-SES - any colorectal cancer	9	1.10	(0.95, 1.27)	71.9	
Sex					0.0
Combined both sexes	7	1.06	(0.88, 1.26)	76.1	
Females	2	1.26	(0.90, 1.77)	62.8	
Males	0	-	-	-	
Continents					78.5
Europe & others	2	0.72	(0.42, 1.24)	85.8	
North America	7	1.17	(1.09, 1.27)	1.4	
Study design					-
Cohort study	9	1.10	(0.95, 1.27)	71.9	
Case-control	0	-	-	-	
Area-SES - colon cancer	3	1.09	(1.00, 1.19)	0.0	
Area-SES - rectal cancer	3	1.04	(0.57, 1.87)	91.9	
Sex					0.0
Combined both sexes	2	0.85	(0.36, 2.03)	95.2	
Females	1	1.56	(1.08, 2.27)	-	
Males	0	-	-	-	
Continents					100.0
Europe & others	1	0.54	(0.39, 0.75)	-	
North America	2	1.36	(1.15, 1.62)	0.0	
Study design					-
Cohort study	3	1.04	(0.57, 1.87)	91.9	
Case-control	0	-	-	-	
Area-SES - colorectal cancer	3	1.18	(1.00, 1.40)	0.0	

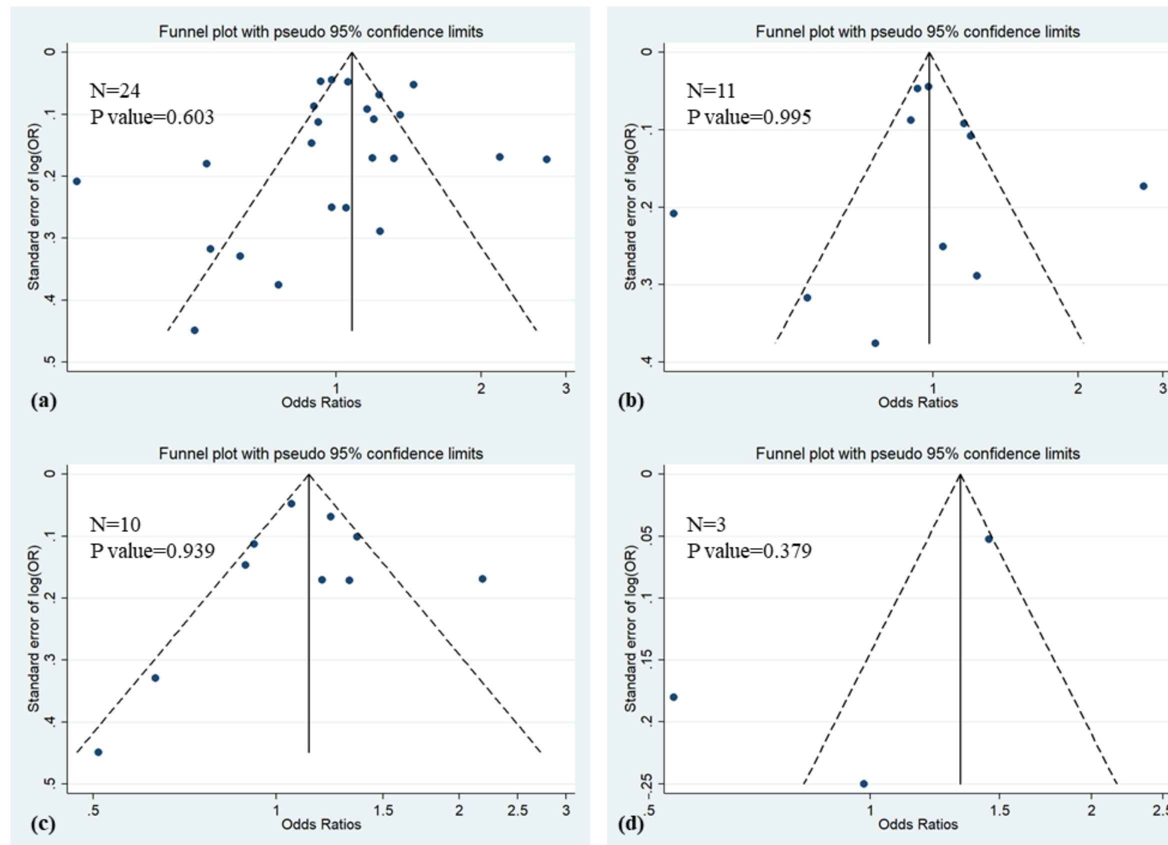


Figure 4.5 Funnel plots and Egger tests of the association between educational attainment and risk of colorectal cancer (a) colon, rectal and colorectal cancers, (b) colon cancer, (c) rectal cancer and (d) colorectal cancer

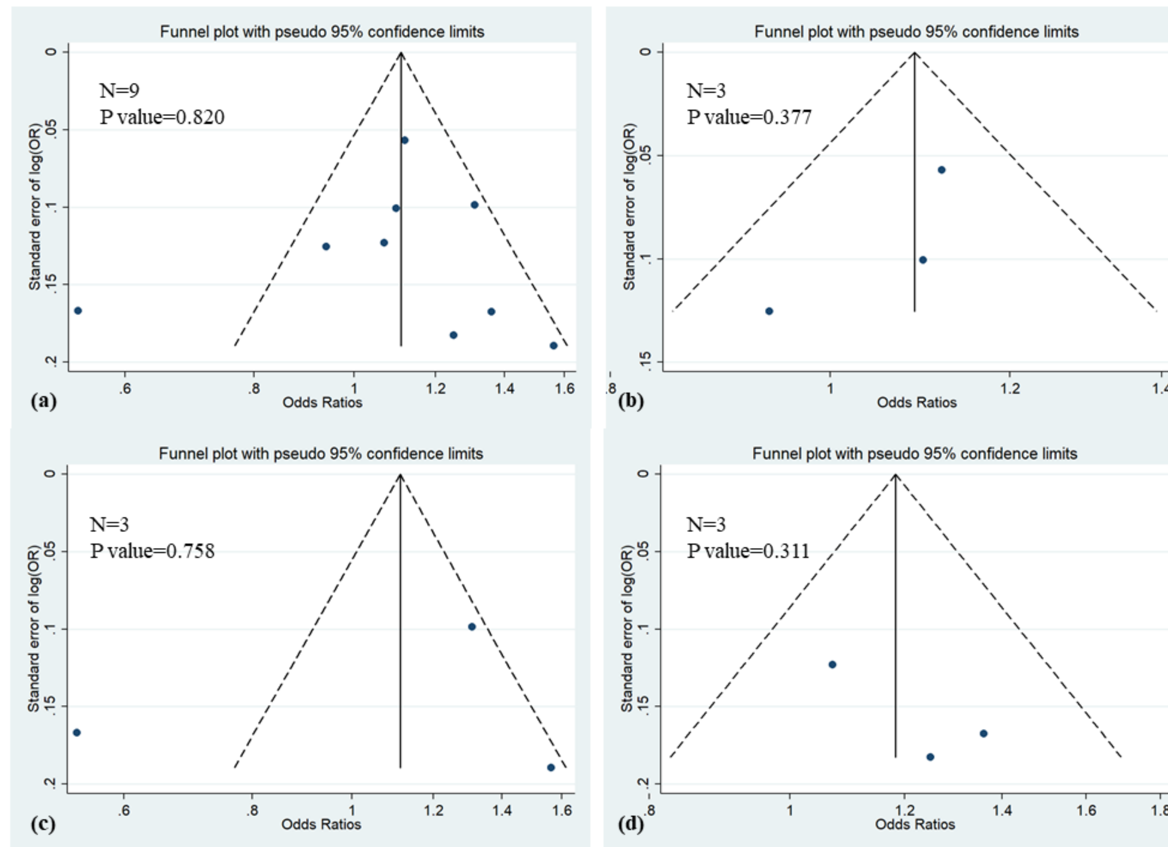


Figure 4.6 Funnel plots and Egger tests of the association composite indicator based on area of residence and risk of colorectal cancer (a) colon, rectal, and colorectal cancers, (b) colon cancer, (c) rectal cancer and (d) colorectal cancer

4.4. Discussion

This review investigated the association between socioeconomic status and risk of colorectal cancer. I found no explicit evidence that people with a lower socioeconomic status (educational attainment and composite socioeconomic status indicators based on area of residence) had greater risk of colorectal cancer. Continent in which studies were conducted and study design partially explained the heterogeneity between studies of the association between socioeconomic status (educational attainment and composite socioeconomic status indicators based on area of residence) and colorectal cancer risk.

In previous reviews on this association between colorectal cancer risk and socioeconomic status[71, 72, 152, 211], authors described characteristics of the associations but did not sum up the overall estimates. There was a high level of heterogeneity between the included studies, partially explained by the continent in which studies were conducted and their design. I attempted to minimise the effect of heterogeneity by conducing subgroup analyses based on continent in which studies were conducted and study design. The previous reviews[71, 72] reported that people with the most deprived socioeconomic status in North America likely had higher risk of colorectal cancer compared to those in the least deprived group, whereas European studies reported opposite results. I argued that the magnitude of the association between socioeconomic status and colorectal cancer risk depends on the socioeconomic status indicator which is used. From the subgroup analyses, people with lower educational attainment in North America had greater risk of developing colorectal cancer, while, lower educational attainment group in Europe had lesser risk of colorectal cancer. Nevertheless, people who lived in the most deprived area in Europe had greater risk of developing colorectal cancer compared to those who lived

in the least deprived area. Study design, especially cohort design, can explain the heterogeneity between studies. Among observational studies, cohort studies have the highest internal validity and therefore the most precise measure of association. So, in meta-analyses of cohort studies, the heterogeneity between studies can be expected to be lower compared to meta-analyses of other observational study designs.

Earlier reviews(71, 72) hypothesised that the prevalence of obesity, smoking and screening uptake differed by study and these differences were driving the heterogeneity of the association between socioeconomic status and risk of colorectal cancer. In fact, these health behaviours do vary across countries and have an impact on the incidence of colorectal cancer. The diverse study populations, health behaviours and screening programs have certainly changed over time; these factors relate to the year of data collection, thus contributing to the heterogeneity between the studies. In this review, there was a wide range in the year of data collection (1945–2012) and I can see from several studies that gaps of socioeconomic disparities were either wider(235) or narrower(217, 244, 245) over different time periods.

There is no best proxy for socioeconomic status, as each measure has its own strengths and limitations(246). Educational attainment reflects the overall knowledge-related assets of individual, including health literacy(78). However, the influence of educational attainment via health literacy is less likely to effect colorectal cancer risk because the cancer risk is more likely embedded with in health behaviours. Generally, income reflects financial resources that can improve health indirectly by increasing the health-promoting environment, promoting consumption of health-enhancing commodities and facilitating access to health services(74). Nonetheless, using income alone as a proxy of

socioeconomic status raises concerns about reverse causation (e.g. colorectal cancer can lead to unemployment), rapid change, and the accuracy of the self-reported income[162]. Most recent studies use composite socioeconomic status indicators based on area of residence as a proxy of socioeconomic status. These composite indicators can be used as an outcome, a primary exposure or an adjustment variable[162]. The mechanisms of the association between a composite socioeconomic status indicator and colorectal cancer risk may differ with differential access to healthcare. For example, colorectal cancer screening uptake may differ across geographic areas according to a variety of health behaviours influenced by access to public transport or automobile parking, or number of grocery stores or fast food shops. For these reasons, underestimation of the true individual-level effect is a major concern when using composite measures of socioeconomic status[74].

For educational attainment in this review, the association was not clear established with a high degree of heterogeneity, mainly attributable to the continent in which the studies were conducted. Some studies (e.g. those conducted in the United States) reported people with low educational attainment being at increased risk especially for rectal cancer while other studies (e.g. those conducted in Italy) reported people with high educational attainment being at increased risk. These observations point to the complexity of socioeconomic risk factors driving colorectal cancer risk. Without access to the individual level data from these studies, it is not possible to investigate the role of potential mediators and confounders that may provide some explanation for this heterogeneity. It is possible that educational attainment in Italy reflects different risk factors for colorectal cancer comparing to the United States, for example, lifestyle and the screening uptake. One of the Italian studies [227], which reported that people with higher educational attainment had

greater risk of colon cancer, provided a discussion on the complex mixture of diet and lifestyle factors as they relate to colon cancer. There was the evidence of high consumption of vegetables and fruit as well as meat among higher social classes in Italy[229, 247]. Moreover, Tavani[227] hypothesised that the group with occupational low physical activities, which tends to be correlated with higher educational attainment and social class, likely has increased risk of colon cancer. On the other hand, one[141] of the United States' studies, which demonstrated the increasing risk of rectal cancer among lower socioeconomic group, proposed that lower colorectal cancer screening uptake might likely be a possible reason for the socioeconomic disparities on risk of colorectal cancer.

The magnitude of the association between educational attainment and risk of rectal cancer was stronger than the association between educational attainment and risk of colon cancer. There are few possible explanations for this finding. Firstly, lower socioeconomic status group has lesser routine colorectal cancer screening uptake compared to the higher socioeconomic status group. They are likely diagnosed with colorectal cancer when they develop the symptoms such as rectal bleeding which is one of the common symptoms for rectal cancer. Secondly, colonoscopy, which explores the whole colon, is more expensive and might have greater out-of-pocket cost compared to sigmoidoscopy, which investigates only sigmoid and rectum. Lower socioeconomic group might be prefer to do sigmoidoscopy than colonoscopy.

Under or over-adjustment of mediators or confounding factors might bias the association between socioeconomic status and colorectal cancer risk. Three studies used mediation analysis in an attempt to determine the causes for the association observed between

socioeconomic status and colorectal cancer risk[79, 80, 223]. These suggested that health behaviours (obesity and smoking) might be mediating the association. Several studies in this review were adjusted for these possible mediators; this may have reduced or distorted the real association between socioeconomic status and colorectal cancer risk. Moreover, this might generate heterogeneity between studies adjusted for possible mediators versus studies which did not perform this adjustment. Recent studies of the association between socioeconomic status and risk of colorectal cancer used data linkage between cancer registries for cases and census data for socioeconomic status indicators. The characteristics of the participants in these studies are age and sex, while other mediators and confounding factors such as health behaviours and family history of colorectal cancer are not available.

A strength of this review is its comprehensive and detailed analysis of the association between socioeconomic status and risk of colorectal cancer that builds on previous reviews. It provided greater detail compared with the previous four reviews[71, 72, 152, 211] by assessing risk of cancer by site within the colorectum (colon, rectum and colorectum combined) and assessing three measures of socioeconomic status (income, education and composite socioeconomic status indicators based on area of residence). Moreover, I included subgroup analyses with reduced heterogeneity, thus the overall estimate for each association is likely to be more consistent. Additionally, my meta-analysis provided an evidence of the geographical effect (continent in which studies were conducted) on the heterogeneity of the association between socioeconomic status and colorectal cancer risk. However, there were few limitations in this review. Firstly, small sample size of ORs for each proxy of socioeconomic status and each cancer site likely reduced power of the study. Secondly, around 40% of all included studies of the association between

socioeconomic status and risk of colorectal cancer and most of the included studies of the association between income level and colorectal cancer risk were cross-sectional studies that were not included to the meta-analysis. The decision to exclude cross-sectional studies from the meta-analysis was driven by: (i) the fact that cross-sectional design, by definition lacks a temporal relationship between the exposure and the outcome and is more exposed to bias than the cohort design and (ii) the fact that my literature search strategy was able to identify a sufficient number of cohort studies that met the inclusion criteria of the review.

Socioeconomic disparities on colorectal cancer risk continue to be an issue across the globe, but not consistently; the strength (and even the direction of the association) varies by the continent in which studies were conducted. To improve our understanding of the role of socioeconomic disparities on colorectal cancer worldwide, universal proxies of socioeconomic status are needed to standardise analyses, and individual level data including measurement of confounding factors is needed.

Chapter 5. Socioeconomic Disparities in Colorectal Cancer Screening Uptake Mediated via Health Behaviours

5.1. Introduction

Colorectal cancer is a major cause of morbidity and mortality in middle- and high-income countries[50]. Randomised controlled trials and observational studies have consistently demonstrated that regular screening, with FOBT or endoscopy, reduces colorectal cancer incidence and mortality[26, 248-250]. However, in the vast majority of countries with a high burden of colorectal cancer, population participation to screening – whether opportunistic or via organised programs – remains low[155, 251, 252]. Across countries, people in the most disadvantage socioeconomic status groups in the population report the lowest level of screening participation. This social gradient has been consistently documented, including in settings where colorectal cancer screening is offered free to the population[202].

Australia launched its National Bowel Cancer Screening Program (NBCSP) in 2006. Participation in the program has been low since its introduction (around 40%). But Australians in lowest socioeconomic status groups have consistently reported the lowest participation rates, the highest positivity rates, lower diagnostic follow-up rates and higher age-standardised incidence and mortality rates, compared to Australians in higher socioeconomic status groups[253].

The factors mediating the association between socioeconomic status and colorectal cancer screening participation are not well understood. Currently, most of the studies investigating these mediators have focused mainly on psychological factors, such as perceived barriers, self-efficacy, fatalism and social norms[254-256]. Few studies have evaluated the potential effects that poor health behaviours may contribute to the association between socioeconomic status and screening participation. There is some evidence that people in lower socioeconomic status groups have poor health behaviours, for example, greater proportion who are smokers[94-101] and higher body mass index[91-93]. Studies have also suggested that smokers[102-107] and obese adults[108-110] are less likely to participate in colorectal cancer screening. A clearer understanding of the extent to which lifestyle factors such as smoking status and body mass index mediate the association between socioeconomic status and colorectal cancer screening is needed to inform whether health promotion strategies targeting health behaviours might be an avenue to increase screening participation.

In this study, I used data from a sample of Australian adults eligible for colorectal cancer screening to examine the association between socioeconomic status indicators and screening participation; and to examine whether the relationship between socioeconomic status and colorectal cancer screening is mediated by a set of lifestyle factors related to health behaviour.

5.2. Methods

5.2.1. Study population

Data were provided by participants to the Australasian Colon Cancer Family Registry, a large population-based cohort study established to address research questions in colorectal cancer aetiology and prevention. Details of the design, methods and recruitment criteria of the Australasian Colon Cancer Family Registry have been provided elsewhere(111). Briefly, participants were recruited via population-based case- and control-probands. Case-probands were residents of the Melbourne metropolitan area who were diagnosed with an incident first primary adenocarcinoma of the colon or rectum at aged between 18 and 59 years and registered to the Victorian Cancer Registry between 1997 and 2007. Attempts were made to recruit their adult first- and second-degree relatives as well as their spouses or partners. Population control-probands were: identified from the federal electoral roll; frequency-matched to the age and sex of the case-probands; registered as living in the Melbourne metropolitan area; and having no prior diagnosis of primary adenocarcinoma of the colon or rectum. Attempts were made to follow-up all participants every four to five years to update their screening history, cancer diagnoses and family history. For this analysis, I included 6,025 population-based the Australasian Colon Cancer Family Registry participants interviewed by follow-up questionnaire between 1997 and 2012 and who completed a risk-factor questionnaire including items on colorectal cancer screening over the previous five years. After excluding those reporting a history of colorectal cancer, bowel disease and any other cancer; those aged under 40 years at time of recruitment; those reporting a non-Caucasian ancestor; and those

having missing on colorectal cancer screening outcome, there were 2,114 Caucasian population-based participants who were aged 40 and older from 819 families (Figure 5.1).

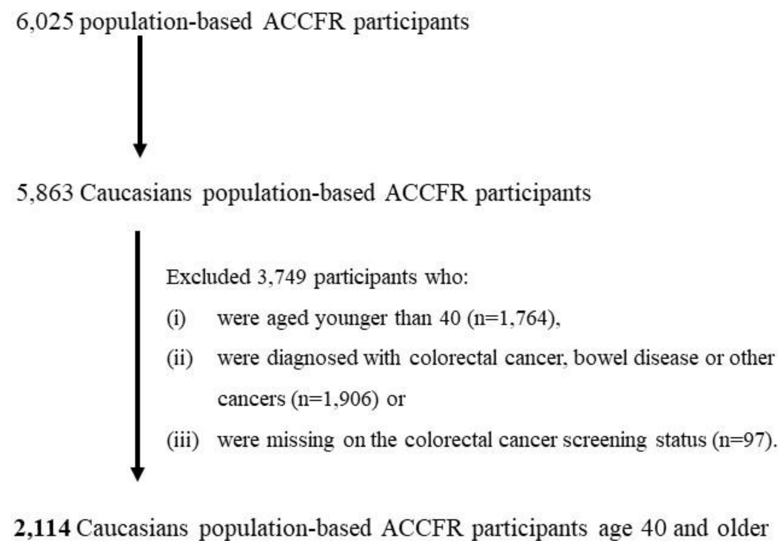


Figure 5.1 Study population

5.2.2. Causal structure of the mediation analysis model

Figure 5.2 summarises my assumptions about the association between socioeconomic status (educational attainment and area of residence) and colorectal cancer screening uptake as well as the potential confounders and mediators of the association (and their confounders). It illustrates the variables that are included in my modelling to estimate unconfounded direct and mediated effects. The justifications for these proxy measures of socioeconomic status are: that people with higher educational attainment are more likely to have stable employment with higher income; and area of residence captures the local areas income and education which correlated with neighbours' socioeconomic status. I have assumed that the direction of this association is from socioeconomic status to healthy

lifestyles rather than vice versa. It is less likely that indicators of health behaviour (such as smoking and obesity in particular) cause indicators of socioeconomic status (such as educational attainment and area of residence). Evidence for obesity and smoking to be potential mediators is that people with high educational attainment or living in least deprived area are more likely to have healthy lifestyles with a higher rates of normal body mass index[91-93] and lower rates of smoking[94-101]. Studies have also reported that smokers[102-107] and obese adults[108-110] may be less likely to participate in colorectal cancer screening. Therefore, obesity and smoking meet the necessary criteria to be considered as possible mediators for the association between socioeconomic status and screening uptake. I assumed that the confounders are age, sex and race because they are potential causal factors of both the exposure (socioeconomic status) and the outcome (colorectal cancer screening uptake). I considered family history of colorectal cancer as a potential confounder of the mediators and the outcome in this analysis based on the assumption that having a family history of colorectal cancer might increase the likelihood of receiving colorectal cancer screening. Similarly, it might also increase the likelihood of seeking clinical advice for a range of health behaviour including obesity and smoking (people with a family history of colorectal cancer might try to reduce their increased risk of colorectal cancer by reducing body weight and not smoking).

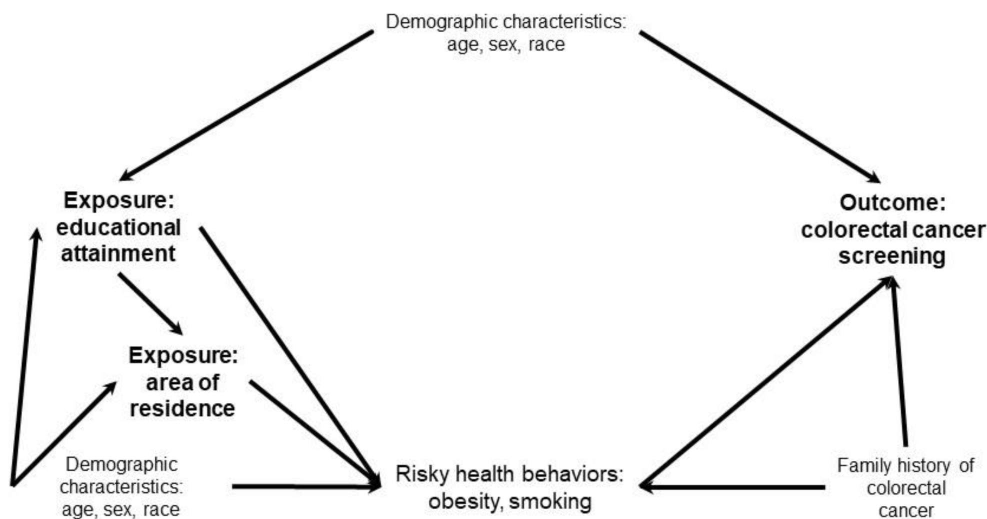


Figure 5.2 Directed acyclic graph of the association between socioeconomic status and colorectal cancer screening uptake that is mediated by smoking and obesity.

5.2.3. Exposures and outcome

I defined indicators of socioeconomic status in two ways: as years of schooling completed (educational attainment); and as IRSD (area of residence). The Australasian Colon Cancer Family Registry collected educational attainment data using a questionnaire item asking "What was the highest level of education that you completed?": I converted this data to an ordinal variable as follows: "primary school"=6 years; "year 7 or 8"=7.5 years; "year 9 or 10"=9.5 years; "year 11 or 12"=11.5 years; "vocational training"=12.5 years; "started but did not graduate from university"=13 years; and "graduated from university"=15 years. IRSD is a composite socioeconomic status indicator based on area of residence and defined by participants' Australians residential postcode[112]. The IRSD for each postcode is calculated by the Australian Bureau of Statistics[112] and based on national census data of employment, income and education. It is consisted of: core variables of socioeconomic status, direct measures of disadvantage and reflect measures of disadvantage. The

Australasian Colon Cancer Family Registry participant's postcode was linked to the SEIFA database for the year 2001 because this was the year of available SEIFA data most concurrent with data collection timeframes for the census and the Australasian Colon Cancer Family Registry. The IRSD were categorized in quintiles based on the distribution of the state in which the participant was living[112].

Colorectal cancer screening uptake was defined as having ever screened by FOBT, sigmoidoscopy or colonoscopy. Screening was distinguished from diagnostic test using the responses to a question of participants by the Australasian Colon Cancer Family Registry asking the reason for the test: "What were the reasons for your first test?". The tests were defined as screening when the reported purpose for any test was family history of colorectal cancer or routine or yearly exam or check-up. If the reasons given for test uptake was not reported, status was categorised as missing.

5.2.4. Potential mediators

Potential mediators in this analysis were the health-related lifestyle behaviours (body mass index and smoking). Body mass index was calculated by weight in kilograms divided by height in metres squared reported by participants at the time of the questionnaire. For smoking, pack-years of smoking was calculated by multiplying the number of packs of cigarettes per day (assumed 20 cigarettes per pack) by total number of years of smoking.

5.2.5. Statistical analysis

A logistic regression analysis was performed to estimate the association, as OR with corresponding 95% CI, between each socioeconomic indicator (either years of schooling

or quintile groups of IRSD) and colorectal cancer screening ever (yes/no) adjusted by the possible confounders: age, sex and number of first-degree relatives with colorectal cancer.

Mediation analysis aims to estimate the direct effect from an exposure to an outcome and the indirect effect via a mediator. A mediator occurs in a causal pathway from an exposure to an outcome. It is assumed to cause (at least partly) the outcome and is assumed to be caused (at least partly) by the exposure[113, 114]. In this context, mediation analysis based on the counterfactual framework was adopted. In brief, the counterfactual framework rests on potential outcomes that cannot be observed[120, 126] and performs modelling on both observed and potential outcomes. The main interest of the analysis is to describe the etiological mechanisms (by quantifying the natural direct and indirect effects of different exposures) behind an outcome of interest. The natural direct effect demonstrates how much the outcome would change if the exposure were changed but the mediator was kept at the level at which it would be if each individual received no exposure[118, 129]. The natural indirect effect shows how much the outcome would change on average with no exposure[129] or with exposure[118] and by changing the mediator to whatever value it would attain for each individual under the condition of having exposure[118, 129]. The summation of natural direct and indirect effect is the total effect. The proportion mediated is calculated as the ratio of the natural indirect effect to the total effect. This proportion mediated reflects how much the effect of an outcome would change if the pathway from the exposure to the mediators is prevented[115]. In practical, the proportion mediated is calculated by using the formula proposed by Ferguson and colleagues[131]:

$$100\left(\frac{lnOR_{NIE}}{lnOR_{NDE} + lnOR_{NIE}}\right)$$

A causal interpretation of the natural direct and indirect effects requires four assumptions[115, 118]: (a) there exists no unmeasured confounder of the exposure–outcome relationship, (b) no unmeasured confounder of the mediator–outcome relationship, (c) no unmeasured confounder of the exposure–mediator relationship and (d) no mediator–outcome confounder that is affected by the exposure. Additionally, an assumption of temporal ordering that assumes that the exposure occurs before the mediator, and that they both precede the outcome is essential for assumptions (a), (b) and (c). To investigate how robust the results are to the violation of these assumptions, I conducted a sensitivity analysis based on the correlated residual method developed by Imai[133, 134]. The sensivity parameter ρ is the correlation between the error for the mediation model and the error for the outcome model[132, 133, 135]. Under those assumptions ρ is zero. If there is any omitted variable that affects both the mediator and the outcome variables, the omitted variable is part of the two error terms; therefore, the value of ρ will be greater or less than zero, which reflects departure from those assumptions. When the assumptions are unlikely to be satisfied, the range of sensitivity parameter ρ and the mediated effect are (–1, 1) and (–∞, ∞), respectively[132].

Stata 14 was used for descriptive analyses, regression and causal mediation analyses. All analyses included a cluster subcommand to account for non-independence of relatives in the sample. The Stata mediation analysis package (*medeff* and *medsens*)[135] based on a counterfactual approach was used in this analysis. The *medeff* command simulates the predicted values of the mediator or outcome variable, which are not observed, and calculates the average causal mediation, direct and total effects. The uncertainty estimates are based on the quasi-Bayesian Monte Carlo approximation[135]. The *medsens* command calculates ρ which indicates how robust the results are to the violation of the assumptions

and provide the plots between estimated average mediated effect and ρ. To get ORs of indirect effect, which is the magnitude of the mediated effect, I used *paramed* command. The *paramed* performs causal mediation analysis using parametric regression models based on a counterfactual approach[118, 138]. It estimates ORs for the natural direct, natural indirect and total effects with 95% CIs derived using the delta method[138].

I conducted the mediation analyses separately for each socioeconomic status indicators (educational attainment and IRSD) and each mediator (body mass index and pack-years of smoking). The socioeconomic status indicators used for the *medeff* command were year of schooling and quintile groups of IRSD. For the *paramed* command, I used binary socioeconomic status indicators which were educational attainment level of university and higher (yes/no) and 3rd–5th quintile groups of IRSD (yes/no).

5.3. Results

5.3.1. Characteristics of the participants

Of the 2,114 Australasian Colon Cancer Family Registry participants meeting the inclusion criteria, 525 participants reported screening for colorectal cancer. The proportion of colorectal cancer screening uptake was 24.8% (95% CI 23.0%, 26.7%). Table 5.1 shows the study participants' characteristics by colorectal cancer screening uptake. The average ages of colorectal cancer screeners and non-screeners were 54.3 years old (SD 9.8 years) and 56.9 years old (SD 12.2 years), respectively. More than half of both groups were females. The average years of schooling was 11.9 years (SD 2.5 years) for colorectal cancer screeners and 11.4 years (SD 2.6 years) for non-screeners. Approximately one-third of the population in both groups lived in the highest

socioeconomic status area (5th quintile group of IRSD). More than half (57.1%) of non-screeners had at least one first-degree relatives with colorectal cancer, compared with 13.6% of screeners. The average body mass index was 25.6 kg/m2 (SD 4.5 kg/m2) for the screeners and 26.2 kg/m2 (SD 4.9 kg/m2) for the non-screeners. The average pack-years of smoking of the screeners and non-screeners were 9.3 pack-years (SD 15.1 pack-years) and 12.1 pack-years (SD 18.3 pack-years), respectively.

5.3.2. Educational attainment and colorectal cancer screening uptake

Table 5.2 shows the results of the univariable and multivariable analyses of the association between socioeconomic status indicators and colorectal cancer screening uptake. The odds of colorectal cancer screening uptake increased by 9% (OR 1.09, 95% CI 1.04, 1.16) for each additional year of schooling (educational attainment as a continuous variable); and by 52% (OR 1.52, 95% CI 1.13, 2.03) for people with university educational attainment compared to those whose education stopped before university (educational attainment fitted as a dichotomous variable), after adjusting for age, sex, and number of first-degree relatives with colorectal cancer (Table 5.2).

When the body mass index was tested as a potential mediator of these associations by adding it to the model, the magnitude of the associations between educational attainment and screening uptake did not materially change for the continuous (OR 1.09) or dichotomous measure of educational attainment (OR 1.51) (Table 5.2). The estimates for the proportion mediated effects of body mass index were small; 4.9% for educational attainment as a continuous variable (Table 5.3) and 0% for educational attainment as a dichotomous variable (Table 5.4).

Table 5.1 Characteristics of 2,114 participants by history of colorectal cancer screening.

		Screeners (n=525)		**Non-screeners (n=1.589)**	
		n	**(%)**	**n**	**(%)**
Age					
	Mean ± SD	54.3 ±9.8		56.9 ±12.2	
	Median	53		54	
	Min–Max	40–88		40–93	
Sex					
	Female	295	(56.2)	877	(55.2)
	Male	230	(43.8)	712	(44.8)
Educational attainment					
	Year 8 and below	29	(7.5)	193	(13.5)
	Year 9 or 10	102	(26.5)	347	(24.3)
	Year 11 or 12	71	(18.4)	315	(22.0)
	Vocational training	57	(14.8)	223	(15.6)
	University	126	(32.7)	352	(24.6)
Year of schooling		(n=385)		(n=1,430)	
	Mean ± SD	11.9 ±2.5		11.4 ±2.6	
	Median	11.5		11.5	
	Min–Max	6–15		6–15	
Index of relative socioeconomic disadvantage		(n=499)		(n=1,482)	
	1st quintile (the lowest socioeconomic status)	74	(14.8)	289	(19.5)
	2nd quintile	83	(16.6)	226	(15.3)
	3rd quintile	79	(15.8)	196	(13.2)
	4th quintile	106	(21.2)	291	(19.6)
	5th quintile (the highest socioeconomic status)	157	(31.5)	480	(32.4)
Having 1st degree relatives with colorectal cancer		(n=515)		(n=1,439)	
	No	445	(86.4)	724	(50.3)
	Yes	70	(13.6)	715	(57.1)
Body mass index (kg/m^2)		(n=382)		(n=1,420)	
	Mean ± SD	25.6 ±4.5		26.2 ±4.9	
	Median	24.8		25.4	
	Min–Max	12.3–47.0		16.4–58.3	
Pack-year of smoking		(n=523)		(n=1,581)	
	Mean ± SD	9.3 ±15.1		12.1 ±18.3	
	Median	0.4		1.5	
	Min–Max	0–100		0–100	

Table 5.2 Association between socioeconomic status indicator and colorectal cancer screening uptake

	Univariable		Multivariable*		Multivariable* with body mass index		Multivariable* with pack-years of smoking	
Educational attainment	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Year of schooling	(n=1,815)		(n=1,671)		(n=1,654)		(n=1,666)	
	1.08	(1.03, 1.13)	1.09	(1.04, 1.16)	1.09	(1.03, 1.16)	1.08	(1.02, 1.14)
Educational level	(n=1,815)		(n=1,671)		(n=1,654)		(n=1,666)	
Less than university	1		1		1		1	
University	1.49	(1.14, 1.95)	1.52	(1.13, 2.03)	1.51	(1.13, 2.03)	1.40	(1.04, 1.88)
IRSD								
Quintile groups	(n=1,981)		(n=1,826)		(n=1,540)		(n=1,819)	
	1.03	(0.97, 1.11)	1.09	(1.01, 1.18)	1.06	(0.97, 1.16)	1.08	(1.00, 1.16)
IRSD group	(n=1,981)		(n=1,826)		(n=1,540)		(n=1,819)	
Low socioeconomic status (1st–2rd quintile groups)	1		1		1		1	
High socioeconomic status (3rd–5th quintile groups)	1.16	(0.93, 1.45)	1.36	(1.06, 1.74)	1.26	(0.95, 1.67)	1.32	(1.03, 1.69)

Adjusted by age, sex and number of first degree relative with colorectal cancer

When smoking was tested as a potential mediator of these associations by adding it to the model, the magnitude of these associations did not materially change for the continuous measure of educational attainment (OR 1.08) but did decrease for the dichotomous measure of educational attainment (OR 1.40) (Table 5.2). The estimates for the proportion mediated effects of smoking were 13.7% for educational attainment as a continuous variable (Table 5.5) and 29.4% for education as a dichotomous variable (Table 5.6).

5.3.3. IRSD and colorectal cancer screening uptake

The odds of colorectal cancer screening uptake increased by 9% (OR 1.09, 95% CI 1.01, 1.18) for each additional quintile of IRSD (IRSD fitted as a continuous variable); and by 36% (OR 1.36, 95% CI 1.06, 1,74) for people in the highest quintiles of IRSD (Q3-Q5) versus the lowest quintiles of IRSD (Q1-Q2) (IRSD fitted as a binary variable), after adjusting for age, sex, and number of first-degree relatives with colorectal cancer (Table 5.2).

When body mass index was tested as a potential mediator of these associations by adding it to the model, the magnitude of the associations between IRSD and screening uptake decreased marginally for the continuous (OR 1.06) and dichotomous measure of IRSD (OR 1.26) (Table 5.2). The estimates for the proportion mediated effects of body mass index were 10.2% for IRSD as a continuous variable (Table 5.3) and 7.9% for IRSD as a dichotomous variable (Table 5.4).

When smoking was tested as a potential mediator of these associations by adding it to the model, the magnitude of these associations did not materially change for the continuous measure of IRSD (OR 1.08) or the dichotomous measure of IRSD (OR 1.32) (Table 5.2).

The estimates for the proportion mediated effects of smoking were 15.5% for IRSD as a continuous variable (Table 5.5) and 6.8% for IRSD as a dichotomous variable (Table 5.6).

5.3.4. Sensitivity analysis

The sensitivity analyses of the mediated effect of body mass index on the association between socioeconomic status indicators and colorectal cancer screening uptake using *medsens* command (Figure 5.3) showed that for the point estimate of the average mediated effect to be zero, the correlation between error terms of the regression of body mass index and regression of colorectal cancer screening uptake (ρ) was approximately -0.1. Similarly, the ρ-values were approximately -0.1 for the sensitivity analyses of mediated effect of pack-years of smoking on the association between socioeconomic status indicators and colorectal cancer screening uptake (Figure 5.4). The required assumptions for causal inference of the mediation analyses were not met fully in these models because the ρ departed from 0. These ρ values indicate that there may be variables omitted in these analytic models, which affect both the mediator and the outcome variables.

Table 5.3 Average direct effects of socioeconomic status indicators on colorectal cancer screening uptake and average mediated effects of body mass index (*medeff* command)

	Multivariable*		Average direct effect		Average mediated effect		Total effect		% mediated effect	
	OR	**(95% CI)**	**Est**	**(95% CI)**	**Est**	**(95% CI)**	**Est**	**(95% CI)**	**Est**	**(95% CI)**
Year of schooling	1.09	(1.04, 1.16)	0.0071	(0.0040, 0.0086)	0.0004	(-0.0001, 0.0010)	0.0075	(0.0046, 0.0088)	4.87	(4.28, 8.07)
Quintile groups of IRSD	1.09	(1.01, 1.18)	0.0084	(-0.0045, 0.0201)	0.0011	(-0.0002, 0.0028)	0.0095	(-0.0033, 0.0211)	10.15	(64.89, 104.41)

Adjusted by age, sex and number of first degree relative with colorectal cancer

Table 5.4 Direct effects of socioeconomic status indicators on colorectal cancer screening uptake and indirect effects of body mass index (*paramed* command)

	Screeners		Non-screeners		Multivariable*		Natural direct effect		Natural indirect effect		Total effect		% mediated effect#
	n	**(%)**	**n**	**(%)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	
Educational level													
Less than university	259	(67.3)	1,078	(75.4)	1		1		1		1		
University	126	(32.7)	352	(24.6)	1.52	(1.13, 2.03)	1.52	(1.15, 1.99)	1.00	(0.98, 1.03)	1.52	(1.16, 2.00)	0
IRSD group													
Low socioeconomic status (1st–2rd quintile groups)	157	(31.5)	515	(34.8)	1		1		1		1		
High socioeconomic status (3rd–5th quintile groups)	342	(68.5)	967	(65.3)	1.36	(1.06, 1.74)	1.26	(0.96, 1.65)	1.02	(0.99, 1.05)	1.28	(0.98, 1.68)	7.9

*Adjusted by age, sex and number of first degree relative with colorectal cancer
Calculated by $100(\ln OR_{NIE} / (\ln OR_{NIE} + \ln OR_{NDE}))$

Table 5.5 Average direct effects of socioeconomic status indicators on colorectal cancer screening uptake and average mediated effects of pack-years of smoking (*medeff* command)

	Multivariable*		Average direct effect		Average mediated effect		Total effect		% of mediated effect	
	OR	**(95% CI)**	**Est**	**(95%CI)**	**Est**	**(95%CI)**	**Est**	**(95%CI)**	**Est**	**(95%CI)**
Year of schooling	1.09	(1.04, 1.16)	0.0063	(0.0026, 0.0082)	0.0010	(0.0001, 0.0024)	0.0073	(0.0043, 0.0087)	13.74	(12.00, 23.92)
Quintile groups of IRSD	1.09	(1.01, 1.18)	0.0116	(-0.0006, 0.0230)	0.0022	(0.0006, 0.0041)	0.0138	(0.0017, 0.0250)	15.46	(8.30, 71.17)

*Adjusted by age, sex and number of first degree relative with colorectal cancer

Table 5.6 Direct effects of socioeconomic status indicators on the colorectal cancer screening uptake and indirect effect of pack-years of smoking (*paramed* command)

	Screeners		Non-screeners		Multivariable*		Natural direct effect		Natural indirect effect		Total effect		% mediated effect#
	n	**(%)**	**n**	**(%)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	
Educational level													
Less than university	259	(67.3)	1,078	(75.4)	1		1		1		1		
University	126	(32.7)	352	(24.6)	1.52	(1.13, 2.03)	1.37	(1.04, 1.81)	1.14	(0.99, 1.32)	1.57	(1.16, 2.13)	29.4
IRSD group													
Low socioeconomic status (1st–2rd quintile groups)	157	(31.5)	515	(34.8)	1		1		1		1		
High socioeconomic status (3rd–5th quintile groups)	342	(68.5)	967	(65.3)	1.36	(1.06, 1.74)	1.31	(1.03, 1.66)	1.02	(0.99, 1.05)	1.33	(1.05, 1.70)	6.8

*Adjusted by age, sex and number of first degree relative with colorectal cancer
Calculated by $100(\ln OR_{NIE} / (\ln OR_{NIE} + \ln OR_{NDE}))$

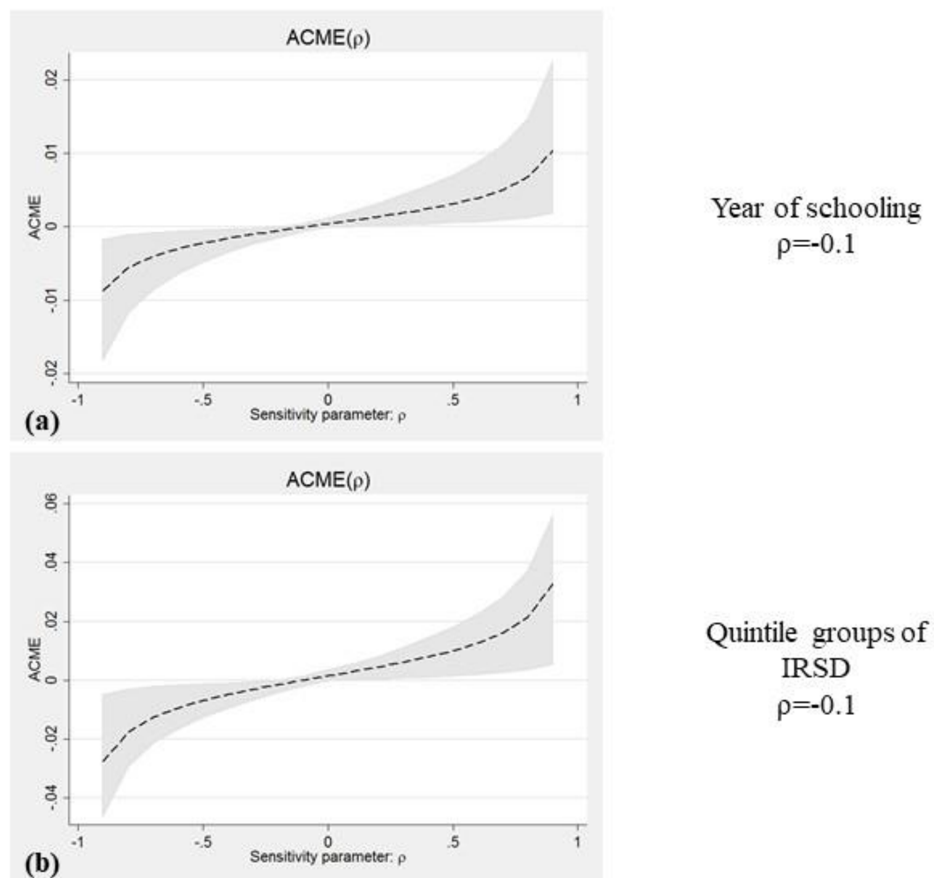


Figure 5.3 Graphical display of sensitivity analyses for mediated effect of body mass index on the association between (a) year of schooling and (b) quintile groups of IRSD and colorectal cancer screening uptake.

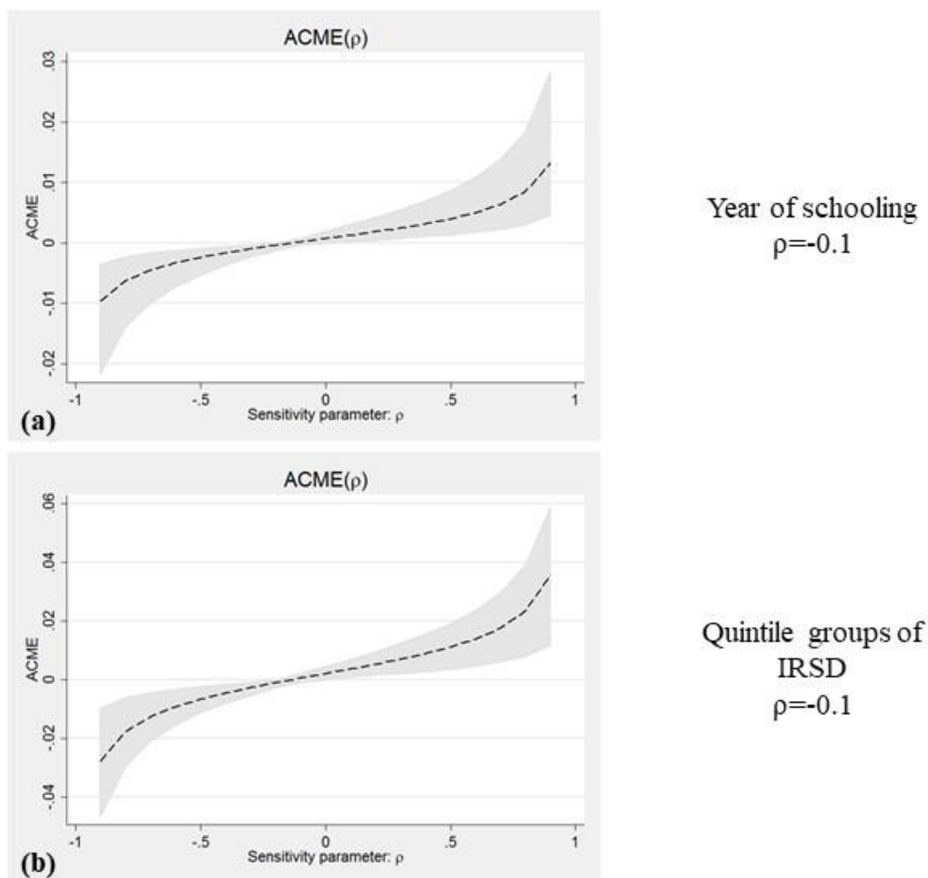


Figure 5.4 Graphical display of sensitivity analyses for mediated effect of pack-years of smoking on the association between (a) year of schooling and (b) quintile groups of IRSD and colorectal cancer screening uptake

5.4. Discussion

In this study, I confirmed the socioeconomic disparities (as assessed by educational attainment and area of residence) in colorectal cancer screening uptake. For each additional year of schooling or each higher quintile of the IRSD, the odds of screening uptake increased approximately 9%. In addition, I found evidence that about 13–15% of this association was mediated effect via smoking (pack-years).

My finding confirmed the socioeconomic disparities in colorectal cancer screening uptake consistent with findings from previous studies in several countries[105, 151, 152, 154, 155, 257]. It should be noted that screening uptake in my study population, at 24%, was low; this may be due to data collection before 2007[111], around the start of the Australian National Bowel Cancer Screening Program in 2006[20]. The socioeconomic disparity in colorectal cancer screening in Australia may decrease over time as the national screening program gains participants; however, ten years after roll-out, uptake for new participants is only 34%, only 10% greater compared to my study population[20].

Causal mediation analysis requires the assumptions of: no exposure-outcome confounders; no exposure-mediator confounders; and no mediator-outcome confounders[115, 118]. In these analyses, some of the confounders (such as age, sex, race and family history of colorectal cancer) were adjusted in the model. However, there are several potential exposure-mediator confounders (i.e. parental socioeconomic status and childhood experience confounders) and mediator-outcome confounders (i.e. accessibility to healthcare and health awareness of the colorectal cancer screening) that I did not include into the model. For example, a low parental income might limit educational attainment of their children and childhood struggle occurring in lower income families likely increases the risk of smoking in later years[99, 258, 259]. Moreover, Australia uses universal health coverage or Medicare for all health services. Accessibility to healthcare might affect screening uptake in this scenario. Limited access to health information and support will prevent both people's smoking cessation and screening uptake. In addition, health awareness might be one of the mediator-outcome confounders. People with health awareness and health concerns may be more likely to do smoking cessation programs and get health checks or screening. I could not include these in my analyses because data on

those possible confounders are not available in the Australasian Colon Cancer Family Registry. The consequence of not adjusting for all potential confounders might be bias of the average causal effect[127, 260]. The sensitivity analyses also suggested that there may be any variable omitted in these analytic models.

Causal inference of the mediation analysis also requires a temporal relationship assumption. The Australasian Colon Cancer Family Registry is a case-control study, so there is no means to test the temporal relationship between exposure and outcome, thereby limiting the evidence for a causal effect. I believe, however, that my assumptions on the temporal relationship between educational attainment, smoking and colorectal cancer screening uptake are reasonable. Generally, people finish their education before aged 30 and colorectal cancer screening for people at average risk is recommended for people aged 50 and older. Moreover, it is also unlikely that screening can affect smoking which is generally initiated prior to age 50. Nevertheless, the temporal relationship between area of residence, smoking and colorectal cancer screening uptake should be considered. Area of residence can change over time for several reasons which may be related to screening, for example moving to get easier access to healthcare, resulting in possible reverse causation.

Smoking is a health behaviour that might be a proxy for people's general awareness of their health, value of their health, and health literacy. In this analysis, I am not suggesting that smoking prevents screening. Rather, I am saying that smoking is a marker of poor health awareness that can explain the association between socioeconomic status and screening uptake. People in socioeconomically deprived groups have low awareness of the contribution of health-related lifestyle factors to cancer[261]. In my analysis, it is likely

that health awareness, which was reflected by health-related lifestyle, affected the screening uptake. Studies have documented the association between low health literacy and lower uptake of cancer screening(262) and how health literacy mediates the association between socioeconomic status and health-related lifestyle behaviours(263). Therefore, health literacy might be the other key explanatory factor of the association between socioeconomic status and colorectal cancer screening uptake.

The Australasian Colon Cancer Family registry is a case- and control- proband based cohort. Its recruitment, by design, oversamples participants who are relatives of colorectal cancer cases. Around, 40 % of the participants have a first degree relative with colorectal cancer, which substantially higher than colorectal cancer cases in general population. Therefore, the finding from my analysis might not be generalisable to the general population.

The strength of this study is the counterfactual approach of mediation analyses. This approach allowed me to adjust for confounders and to use sensitivity analysis to check for potential violations of the causality assumptions. Additionally, I was also able to calculate the proportion of mediated effect which indicates the magnitude of the mediator on the causal pathway. However, there were several unadjusted confounders that might bias the results.

Socioeconomic disparities in colorectal cancer outcomes (not only in screening but also in cancer risk and mortality) are crucial issues in developed countries and will become increasingly important as colorectal cancer incidence increases. Pathways or mechanisms behind the socioeconomic disparities that make complex interactions explicit are needed to develop and implement effective interventions to reduce these disparities.

Chapter 6. Socioeconomic Disparities in Colorectal Cancer Risk Mediated via Health Behaviours and Colorectal Cancer Screening Uptake

6.1. Introduction

Colorectal cancer is a major cause of morbidity and mortality in developed countries. The sociodemographic gradient on colorectal cancer screening, risk and mortality is seen worldwide. However, reviews of the association between socioeconomic status and risk of colorectal cancer found inconsistent results between studies conducted in the United States and other countries[71, 72, 152, 211]. They hypothesised that different colorectal cancer screening programs and health behaviours such as rates of obesity and smoking in each country might be the reasons for the inconsistent results.

Socioeconomic disparities on colorectal cancer screening uptake have been reported globally[105, 151, 152, 154, 155, 257], even in countries offering a free national bowel cancer screening program, for example, Australia[20] and Scotland[264]. In these countries, lower screening uptake rate persists among those in the lowest socioeconomic status groups. Moreover, several randomised controlled trials[26-29] confirmed the effectiveness of endoscopy to reduce colorectal cancer incidence. Participation to regular screening might

therefore be a mediator of the association between socioeconomic status and risk of colorectal cancer.

The other pathways from socioeconomic status to colorectal cancer risk might be routes via health behaviours such as smoking and obesity. Generally, obesity and smoking increase the risk of colorectal cancer. Additionally, there is evidence that people with lower socioeconomic status are at greater risk of smoking[94-101] and higher body mass index[91-93]. The mediated effect of health risk behaviours on the association between socioeconomic status and colorectal cancer were investigated in the United States[79, 80] and Canada[223]. The Canadian study[223] failed to demonstrate the mediated effect of health risk behaviours (smoking, diet and obesity) on the association between educational attainment and risk of colon or rectal cancers but suggested more sophisticated investigations on this topic. The other two United States' studies found the evidence of mediated effect of health behaviours on the association between socioeconomic status and colorectal cancer risk. There were significant mediated effects of red meat intake, alcohol intake and body mass index on the association between neighbourhood socioeconomic status and colon and rectal cancers risk in the Nurses' Health Study[80], Moreover, the association of neighbourhood socioeconomic status and risk of rectal cancer also was mediated via multivitamin use and smoking[80]. From the ongoing prospective NIH-AARP study[79], 43.9% and 36.2% of the colorectal cancer disparities on education and neighbourhood socioeconomic status were mediated via behavioural factors and body mass index.

In this study, I investigated the mediated effect of health behaviours and colorectal cancer screening uptake on the association between socioeconomic status and colorectal cancer risk

in the Australian context by using the counterfactual approach. If the effect of socioeconomic status in colorectal cancer risk is mediated through the screening uptake or health behaviours such as smoking and obesity, interventions to improve these health behaviours and the screening uptake could be a means to help prevent morbidity and mortality from colorectal cancer.

6.2. Methods

6.2.1. Study population

Data were provided by participants to the Australasian Colon Cancer Family Registry, a large population-based cohort study established to address research questions on colorectal cancer aetiology and prevention. Details of the design, methods and recruitment criteria of the Australasian Colon Cancer Family Registry have been provided elsewhere[111]. Briefly, participants were recruited via population-based case- and control-probands. Case-probands were residents of the Melbourne metropolitan area who were diagnosed with an incident first primary adenocarcinoma of the colon or rectum at aged between 18 and 59 years and registered to the Victorian Cancer Registry between 1997 and 2007. Attempts were made to recruit their adult first- and second-degree relatives as well as their spouses/partners. Population control-probands were: identified from the federal electoral roll; frequency-matched to the age and sex of the case-probands; registered as living in the Melbourne metropolitan area; and having no prior diagnosis of primary adenocarcinoma of the colon or rectum. Attempts were made to follow-up all participants every four to five years to update their screening history, cancer diagnoses and family history. For this analysis, I included

6,025 population-based the Australasian Colon Cancer Family Registry participants interviewed by follow-up questionnaire between 1997 and 2012 and who completed a risk-factor questionnaire including items on colorectal cancer screening over the previous five years. After excluding 110 colorectal cancer cases who were missing on screening uptake and their age at colorectal cancer diagnosis before age of the first screening uptake, there were 5,753 Caucasians population-based the Australasian Colon Cancer Family Registry participants from 1,146 families (Figure 6.1).

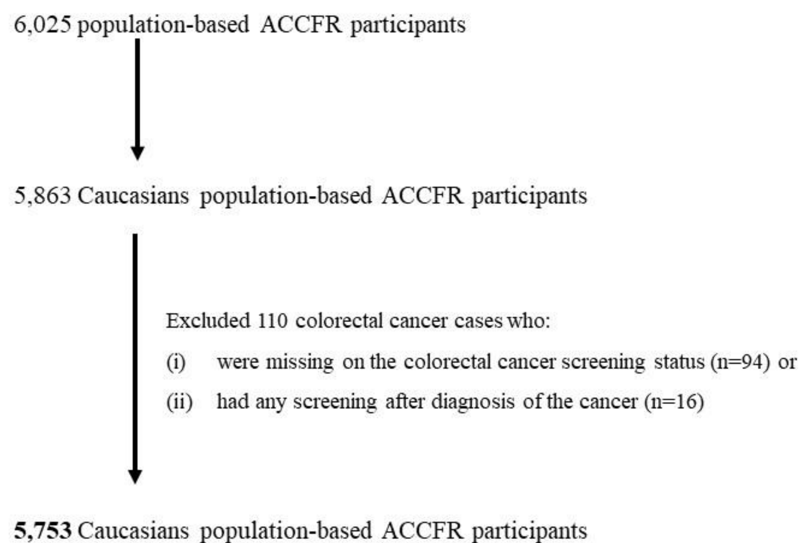


Figure 6.1 Study population

6.2.2. Causal structure of the mediation analysis model

Figure 6.2 summaries my assumptions about the association between socioeconomic status (educational attainment and area of residence) and colorectal cancer risk as well as the

potential confounders and mediators of this association (and their confounders). The causal diagram illustrates the variables included in my modelling to estimate unconfounded direct and mediated effects. The justifications for these proxy measures of socioeconomic status are: that higher educational attainment groups likely have higher income; and area of residence captures the local areas income and education which correlated with neighbours' socioeconomic status. I have assumed that the direction of this association is from socioeconomic status to healthy lifestyles rather than vice versa. It is unlikely that indicators of health behaviour (such as smoking and obesity in particular) cause indicators of socioeconomic status (such as educational attainment and area of residence). Evidence for obesity and smoking to be potential mediators is that people with high educational attainment or living in the least deprived area tend to have healthier lifestyles with a higher rates of normal body mass index[91-93] and lower rates of smoking[94-101]. Studies have also reported that smokers[102-107] and obese adults[108-110] may be less likely to participate in colorectal cancer screening. There was an evidence of socioeconomic disparities in colorectal cancer screening uptake. Lower socioeconomic status groups had lower colorectal cancer screening uptake[156-159]. Generally, these risky health behaviours increase risk of colorectal cancer. Obese adults[59, 66, 253] or smokers[66, 253] have higher risk of colorectal cancer. The effect of colorectal cancer screening on risk of colorectal cancer also depends on the type of screening modality. Screening by endoscopy can decrease the risk of colorectal cancer by polyp removal. Nevertheless, screening is likely to increase the apparent incidence of colorectal cancer in the population in the early stages of the screening program and the incidence will decrease as the screening program matures. Therefore, obesity, smoking and colorectal cancer screening uptake meet the essential criteria to be considered as possible mediators for

the association between socioeconomic status and colorectal cancer risk. I assumed that the confounders are age, sex and race because they are potential causal factors of both socioeconomic status and risk of colorectal cancer. I considered family history of colorectal cancer as a potential confounder of the mediators and the outcomes in this analysis based on the assumption that having a family history of colorectal cancer might increase the likelihood of receiving colorectal cancer screening. Similarly, it might also increase the likelihood of seeking clinical advice for a range of health behaviour including obesity, smoking and cancer screening. In general, people with a first-degree relative with colorectal cancer have an increased risk of colorectal cancer[63].

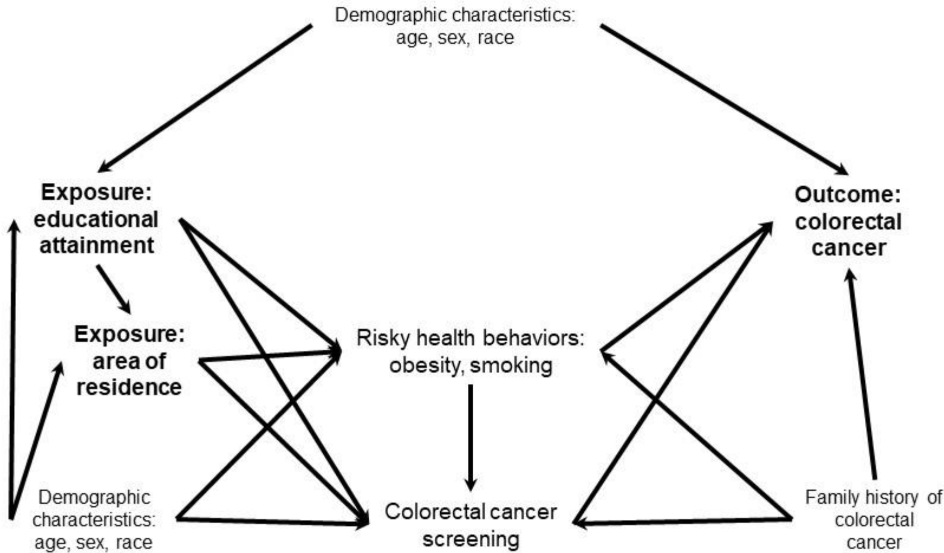


Figure 6.2 Directed acyclic graph of the association between socioeconomic status and colorectal cancer risk that is mediated by colorectal cancer screening uptake, smoking and obesity.

6.2.3. Exposures and outcome

I defined indicators of socioeconomic status in two ways: as years of schooling completed (educational attainment); and as IRSD (area of residence). The Australasian Colon Cancer Family Registry collected educational attainment data using a questionnaire item asking: "What was the highest level of education that you completed?". I converted this data to an ordinal variable as follows: "primary school"=6 years; "year 7 or 8"=7.5 years; "year 9 or 10"=9.5 years; "year 11 or 12"=11.5 years; "vocational training"=12.5 years; "started but did not graduate from university"=13 years; and "graduated from university"=15 years. IRSD is a composite socioeconomic status indicator based on area of residence and defined by participants' Australians residential postcode[(112)]. The IRSD for each postcode is calculated by the Australian Bureau of Statistics[(112)] and based on national census data of employment, income and education. It is consisted of: core variables of socioeconomic status, direct measures of disadvantage and reflect measures of disadvantage. The Australasian Colon Cancer Family Registry participant's postcode was linked to the SEIFA database for the year 2001 because this was the year of available SEIFA data most concurrent with data collection timeframes for the census and the Australasian Colon Cancer Family Registry. The IRSD were categorized in quintiles based on the distribution of the state in which the participant was living[(112)].

The outcome of this analysis was colorectal cancer cases defined as the Australasian Colon Cancer Family Registry participants who were diagnosed as having a primary cancer site at colon or rectum on or after the date of having their first screening uptake or the colorectal

cancer cases who were diagnosed at any point of time if they did not report colorectal cancer screening uptake.

6.2.4. Potential mediators

Potential mediators in this analysis were the health-related lifestyle behaviours (body mass index and smoking) and colorectal cancer screening uptake (any modalities and endoscopy). Body mass index was calculated by weight in kilograms divided by height in metres squared reported by participants at the time of the questionnaire. For smoking, pack-years of smoking was calculated by multiplying the number of packs of cigarettes per day (assumed 20 cigarettes per pack) by total number of years of smoking. Any colorectal cancer screening uptake was defined as having ever screened with FOBT, sigmoidoscopy or colonoscopy. Screening endoscopy was defined as having ever screened with sigmoidoscopy or colonoscopy. Screening was distinguished from diagnostic test using the responses to a question of participants by the Australasian Colon Cancer Family Registry asking the reason for the test: "What were the reasons for your first test?". The tests were defined as screening when the reported purpose for any test was family history of colorectal cancer or routine or yearly exam or check-up. If the reasons given for test uptake was not reported, status was categorised as missing.

6.2.5. Statistical analysis

A logistic regression analysis was performed to estimate the association, as OR with corresponding 95% CI, between each socioeconomic status indicator (either years of

schooling or quintile groups of IRSD) and colorectal cancer risk (yes/no) adjusted by the possible confounders: age, sex and number of first-degree relatives with colorectal cancer.

Mediation analysis aims to estimate the direct effect from an exposure to an outcome and the indirect effect via a mediator. A mediator occurs in a causal pathway from an exposure to an outcome. It is assumed to cause (at least partly) the outcome and is assumed to be caused (at least partly) by the exposure[113, 114]. In this context, mediation analysis based on the counterfactual framework was adopted. In brief, the counterfactual framework rests on potential outcomes that cannot be observed[120, 126] and performs modelling on both observed and potential outcomes. The main interest of the analysis is to describe the etiological mechanisms (by quantifying the natural direct and indirect effects of different exposures) behind an outcome of interest. The natural direct effect demonstrates how much the outcome would change if the exposure were changed but the mediator was kept at the level at which it would be if each individual received no exposure[118, 129]. The natural indirect effect shows how much the outcome would change on average with no exposure[129] or with exposure[118] and by changing the mediator to whatever value it would attain for each individual under the condition of having exposure[118, 129]. The summation of natural direct and indirect effect is the total effect. The proportion mediated is calculated as the ratio of the natural indirect effect to the total effect. This proportion mediated reflects how much the effect of an outcome would change if the pathway from the exposure to the mediators is prevented[115].

A causal interpretation of the natural direct and indirect effects requires four assumptions[115, 118]: (a) there exists no unmeasured confounder of the exposure–outcome relationship, (b) no unmeasured confounder of the mediator–outcome relationship, (c) no unmeasured

confounder of the exposure–mediator relationship and (d) no mediator–outcome confounder that is affected by the exposure. Additionally, an assumption of temporal ordering that assumes that the exposure occurs before the mediator, and that they both precede the outcome is essential for assumptions (a), (b) and (c). To investigate how robust the results are to the violation of these assumptions, I conducted a sensitivity analysis based on the correlated residual method developed by Imai[133, 134]. The sensivity parameter ρ is the correlation between the error for the mediation model and the error for the outcome model[132, 133, 135]. Under those assumptions ρ is zero. If there is any omitted variable that affects both the mediator and the outcome variables, the omitted variable is part of the two error terms; therefore, the value of ρ will be greater or less than zero, which reflects departure from those assumptions. When the assumptions are unlikely to be satisfied, the range of sensitivity parameter ρ and the mediated effect are (–1, 1) and (–∞, ∞), respectively[132].

Stata 14 was used for descriptive analyses, regression and causal mediation analyses. All analyses included a cluster subcommand to account for non-independence of relatives in the sample. The Stata mediation analysis package (*medeff* and *medsens*)[135] based on a counterfactual approach was used in this analysis. The *medeff* command simulates the predicted values of the mediator or outcome variable, which are not observed, and calculates the average causal mediation, direct and total effects. The uncertainty estimates are based on the quasi-Bayesian Monte Carlo approximation[135]. The *medsens* command calculates ρ which indicates how robust the results are to the violation of the assumptions and provide the plots between estimated average mediated effect and ρ. To get ORs of indirect effect, which is the magnitude of the mediated effect, I used *paramed* command. The *paramed* performs

causal mediation analysis using parametric regression models based on a counterfactual approach[118, 138]. It estimates ORs for the natural direct, natural indirect and total effects with 95% CIs derived using the delta method[138].

I conducted the mediation analyses separately for each socioeconomic status indicator (educational attainment and IRSD) and each mediator (body mass index, pack-years of smoking, any colorectal cancer screening uptake and screening endoscopy uptake). The socioeconomic status indicators used for the *medeff* command were year of schooling and quintile groups of IRSD. For the *paramed* command, I used binary socioeconomic status indicators which were educational attainment level of university and higher (yes/no) and 3rd–5th quintile groups of IRSD (yes/no).

6.3. Results

6.3.1. Characteristics of the participants

Of 5,753 participants meeting the inclusion criteria, the proportion with colorectal cancer was 16.1% (95% CI 15.2%, 17.1%). Table 6.1 shows participants' characteristics by colorectal cancer risk. The average age of colorectal cases and non-cases were 50.6 years old (SD 10.8 years) and 47.4 years old (SD 17.2 years) respectively. The proportion of males among the cases (49.6%) was higher comparing to non-cases (43.4%). The average years of schooling was 11.8 (SD 2.4 years) for both cases and non-cases. Distributions of the participants across the quintile groups of IRSD were similar between cases and non-cases, in that around half of the participants lived in the higher socioeconomic status area (4th and 5th quintile area of IRSD). Nearly two-third (63.9%) of the cases had no first-degree relative

with colorectal cancer while nearly one-third (31.5%) of non-cases did. The average body mass index of the cases (27.1 kg/m^2, SD 5.1 kg/m^2) was slightly higher compared to non-cases (25.5 kg/m^2, SD 5.0 kg/m^2). The average pack-years of smoking were 11.6 pack-years (SD 17.9 pack-years) among the cases and 9.1 pack-years (SD 16.3 pack-years) among the non-cases. The proportions of any colorectal cancer screening uptake of cases and non-cases were 10.6% and 24.2% respectively. Similarly, 9.0% of cases and 21.6% of non-cases reported ever having screened with endoscopy.

6.3.2. Educational attainment and risk of colorectal cancer

Table 6.2 shows univariable and multivariable associations between socioeconomic status indicators and risk of colorectal cancer. The associations between colorectal cancer risk and educational attainment were null for years of schooling (OR 1.00, 95% CI 0.96, 1.03) and for educational level of university versus no university (OR 0.95, 95% CI 0.80, 1.12), after adjusting for age, sex and number of first-degree relatives with colorectal cancer. The magnitude of the association between colorectal cancer risk and educational attainment did not change after adding body mass index, pack-years of smoking or colorectal cancer screening uptake to the model.

When body mass index was tested as a potential mediator of these associations by adding it to the model, the magnitude of the associations between educational attainment and colorectal cancer risk did not materially change for the continuous (OR 1.01) or dichotomous measure of educational attainment (OR 0.97) (Table 6.2). The estimates for the proportion mediated effects of body mass index could not be estimated with any useful degree of

precision (extremely wide confidence intervals) and no evidence as differing from zero (Table 6.3 and Table 6.4).

When smoking was tested as a potential mediator of these associations by adding it to the model, the magnitude of these associations decreased but did not change for the continuous measure of educational attainment (OR 1.00) or the dichotomous measure of educational attainment (OR 0.97) (Table 6.2). The estimates for the proportion mediated effects of smoking could not be estimated with any useful degree of precision (extremely wide confidence intervals) and no evidence as differing from zero (Table 6.5 and Table 6.6).

When any colorectal cancer screening was tested as a potential mediator of these associations by adding it to the model, the magnitude of these associations decreased but did not materially change for the continuous measure of educational attainment (OR 1.01) but did decrease for the dichotomous measure of educational attainment (OR 0.99) (Table 6.2). The estimates for the proportion mediated effects of screening could not be estimated with any useful degree of precision (extremely wide confidence intervals) and no evidence as differing from zero (Table 6.7 and Table 6.8).

When endoscopy uptake was tested as a potential mediator of these associations by adding it to the model, the magnitude of the associations decreased but slightly change for the continuous measure of educational attainment (OR 1.01) but did decrease for the dichotomous measure of educational attainment (OR 0.99) (Table 6.2). The mediated effects of endoscopy uptake could not be estimated with any useful degree of precision (extremely wide confidence intervals) (Table 6.9 and Table 6.10).

6.3.3. IRSD and risk of colorectal cancer

Multivariable associations between IRSD and colorectal cancer risk showed no association with colorectal cancer risk for each higher quintile of IRSD as a continuous variable (OR 1.02, 95% CI 0.97, 1.07) or dichotomous variable comparing odds of colorectal cancer in people with higher socioeconomic status (3rd–5th quintile groups) compared to those with lower socioeconomic status (1st–2rd quintile groups) (OR 1.07, 95% CI 0.91, 1.25). The magnitude of the association between colorectal cancer risk and IRSD did not change after adding body mass index, pack-years of smoking or colorectal cancer screening uptake to the model (Table 6.2).

When body mass index was tested as a potential mediator of these associations by adding it to the model, the magnitude of the associations between IRSD and colorectal cancer risk did not materially change for the continuous (OR 1.03) or dichotomous measure of IRSD (OR 1.10) (Table 6.2). The estimates for the proportion mediated effects of body mass index could not be estimated with any useful degree of precision (extremely wide confidence intervals) and no evidence as differing from zero (Table 6.3 and Table 6.4).

When smoking was tested as a potential mediator of these associations by adding it to the model, the magnitude of these associations decreased did not change for the continuous measure of IRSD (OR 1.03) or the dichotomous measure of IRSD (OR 1.08) (Table 6.2). The estimates for the proportion mediated effects of smoking could not be estimated with any useful degree of precision (extremely wide confidence intervals) and no evidence as differing from zero (Table 6.5 and Table 6.6).

When any screening test uptake was tested as a potential mediator of these associations by adding it to the model, the magnitude of these associations decreased but did not materially change for the continuous measure of IRSD (OR 1.03) but did decrease for the dichotomous measure of IRSD (OR 1.09) (Table 6.2). The estimates for the proportion mediated effects of screening could not be estimated with any useful degree of precision (extremely wide confidence intervals) and no evidence as differing from zero (Table 6.7 and Table 6.8)
When endoscopy uptake was tested as a potential mediator of these associations by adding it to the model, the magnitude of these associations decreased slightly for the continuous measure of IRSD (OR 1.02) but did decrease for the dichotomous measure of IRSD (OR 1.08) (Table 6.2). Similar to the any screening test uptake, the mediated effect of screening could not be estimated with any useful degree of precision (extremely wide confidence intervals) and there was no evidence of that effect being different from zero (Table 6.9 and Table 6.10).

Table 6.1 Characteristics of 5,753 participants by colorectal cancer risk

		CRC cases (n=929)		**Non-CRC (n=4,824)**	
		n	**(%)**	**n**	**(%)**
Age					
	Mean±SD	50.6±10.8		47.4±17.2	
	Median	50		48	
	Min–Max	19–90		18–94	
Sex					
	Female	468	(50.4)	2,730	(56.6)
	Male	461	(49.6)	2,094	(43.4)
Educational attainment					
	Year 8 and below	72	(8.5)	381	(8.9)
	Year 9 or 10	190	(22.4)	841	(19.7)
	Year 11 or 12	192	(22.6)	1,176	(27.5)
	Vocational training	156	(18.4)	631	(14.8)
	University	238	(28.1)	1,249	(29.2)
Year of schooling		(n=848)		(n=4,278)	
	Mean±SD	11.8±2.4		11.8±2.4	
	Median	11.5		11.5	
	Min–Max	6–15		6–15	
Index of relative socioeconomic disadvantage					
	1st quintile (the lowest socioeconomic status)	182	(19.9)	830	(18.1)
	2nd quintile	111	(12.1)	733	(16.0)
	3rd quintile	119	(13.0)	667	(14.5)
	4th quintile	194	(21.2)	905	(19.7)
	5th quintile (the highest socioeconomic status)	311	(33.9)	1,451	(31.6)
Having first degree relatives with colorectal cancer					
	No	563	(63.9)	1,429	(31.5)
	Yes	318	(36.1)	3,110	(68.5)
Body mass index (kg/m^2)		(n=839)		(n=4,235)	
	Mean±SD	27.1±5.1		25.5±5.0	
	Median	26.3		24.8	
	Min–Max	14.5–52.7		12.3–63.7	
Pack-year of smoking		(n=928)		(n=4,802)	
	Mean±SD	11.6±17.9		9.1±16.3	
	Median	1.2		0.5	
	Min–Max	0–100		0–100	
Having any screening test					
	No	831	(89.5)	3,497	(75.8)
	Yes	98	(10.6)	1,114	(24.2)
Having screening endoscopy					
	No	843	(91.0)	3,662	(78.4)
	Yes	83	(9.0)	1,010	(21.6)

Table 6.2 Association between socioeconomic status indicator and colorectal cancer risk

	Univariable		**Multivariable***		**Multivariable* with body mass index**		**Multivariable* with pack-years of smoking**		**Multivariable* with having any screening uptake**		**Multivariable* with having screening endoscopy**	
	OR	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Educational attainment												
Year of schooling	(n=5,126)		(n=4,816)		(n=4,759)		(n=4,804)		(n=4,647)		(n=4,696)	
	0.99	(0.96, 1.02)	1.00	(0.96, 1.03)	1.01	(0.97, 1.04)	1.00	(0.97, 1.04)	1.01	(0.97, 1.04)	1.01	(0.97, 1.04)
Educational level	(n=5,126)		(n=4,816)		(n=4,759)		(n=4,804)		(n=4,647)		(n=4,696)	
Less than university	1		1		1		1		1		1	
University	0.95	(0.81, 1.11)	0.95	(0.80, 1.12)	0.97	(0.82, 1.15)	0.97	(0.82, 1.16)	0.99	(0.84, 1.18)	0.99	(0.83, 1.17)
IRSD												
Quintile groups	(n=5,503)		(n=5,178)		(n=4,538)		(n=5,160)		(n=4,982)		(n=5,035)	
	1.03	(0.98, 1.07)	1.02	(0.97, 1.07)	1.03	(0.98, 1.09)	1.03	(0.98, 1.08)	1.03	(0.98, 1.08)	1.02	(0.97, 1.08)
IRSD group	(n=5,503)		(n=5,178)		(n=4,538)		(n=5,160)		(n=4,982)		(n=5,035)	
Low socioeconomic status (1st–2rd quintile groups)	1		1		1		1		1		1	
High socioeconomic status (3rd–5th quintile groups)	1.10	(0.96, 1.26)	1.07	(0.91, 1.25)	1.10	(0.93, 1.30)	1.08	(0.93, 1.26)	1.09	(0.93, 1.28)	1.08	(0.92, 1.26)

Adjusted by age, sex and number of first degree relative with colorectal cancer

Table 6.3 Average direct effects of socioeconomic status indicators on colorectal cancer risk and average mediated effects of body mass index (*medeff* command)

	Multivariable*		Average direct effect		Average mediated effect		Total effect		% of mediated effect	
	OR	**(95% CI)**	**Est**	**95%CI**	**Est**	**95%CI**	**Est**	**95%CI**	**Est**	**95%CI**
Year of schooling	1.00	(0.96, 1.03)	0.0006	(-0.0048, 0.0043)	-0.0011	(-0.0017, -0.0005)	-0.0005	(-0.0060, 0.0034)	19.94	(-682.27, 505.25)
Quintile groups of IRSD	1.02	(0.97, 1.07)	0.0039	(-0.0033, 0.0105)	-0.0024	(-0.0035, -0.0014)	0.0015	(-0.0057, 0.0078)	-50.18	(-971.89, 923.44)

Adjusted by age, sex and number of first degree relative with colorectal cancer

Table 6.4 Direct effects of socioeconomic status indicators on the colorectal cancer risk and indirect effect of body mass index (*paramed* command)

	CRC cases		Non-CRC cases		Multivariable*		Natural direct effect		Natural indirect effect		Total effect	
	n	**(%)**	**n**	**(%)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Educational level												
Less than university	610	(71.9)	3,029	(70.8)	1		1		1		1	
University	238	(28.1)	1,249	(29.2)	0.95	(0.80, 1.12)	0.96	(0.81, 1.15)	0.98	(0.95, 1.00)	0.94	(0.79, 1.12)
IRSD group												
Low socioeconomic status (1st–2rd quintile groups)	293	(32.0)	1,563	(34.1)	1		1		1		1	
High socioeconomic status (3rd–5th quintile groups)	624	(68.1)	3,023	(65.9)	1.07	(0.91, 1.25)	1.11	(0.93, 1.32)	0.95	(0.93, 0.98)	1.06	(0.89, 1.26)

Adjusted by age, sex and number of first degree relative with colorectal cancer

Table 6.5 Average direct effects of socioeconomic status indicators on colorectal cancer risk and average mediated effects of pack-years of smoking (*medeff* command)

	Multivariable*		**Average direct effect**		**Average mediated effect**		**Total effect**		**% of mediated effect**	
	OR	**(95% CI)**	**Est**	**(95%CI)**	**Est**	**(95%CI)**	**Est**	**(95%CI)**	**Est**	**(95%CI)**
Year of schooling	1.00	(0.96, 1.03)	<0.0001	(-0.0057, 0.0040)	-0.0006	(-0.0013, <0.0001)	-0.0006	(-0.0061, 0.0033)	12.78	(-295.03, 370.07)
Quintile groups of IRSD	1.02	(0.97, 1.07)	0.0033	(-0.0032, 0.0093)	-0.0007	(-0.0013, -0.0001)	0.0026	(-0.0038, 0.0084)	-14.88	(-166.00, 247.27)

Adjusted by age, sex and number of first degree relative with colorectal cancer

Table 6.6 Direct effects of socioeconomic status indicators on the colorectal cancer risk and indirect effect of pack-years of smoking (*paramed* command)

	CRC cases		**Non-CRC cases**		**Multivariable***		**Natural direct effect**		**Natural indirect effect**		**Total effect**	
	n	**(%)**	**n**	**(%)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Educational level												
Less than university	610	(71.9)	3,029	(70.8)	1		1		1		1	
University	238	(28.1)	1,249	(29.2)	0.95	(0.80, 1.12)	1.03	(0.85, 1.24)	0.94	(0.89, 0.99)	0.97	(0.81, 1.15)
IRSD group												
Low socioeconomic status (1st–2rd quintile groups)	293	(32.0)	1,563	(34.1)	1		1		1		1	
High socioeconomic status (3rd–5th quintile groups)	624	(68.1)	3,023	(65.9)	1.07	(0.91, 1.25)	1.09	(0.92, 1.28)	0.98	(0.97, 1.00)	1.07	(0.91, 1.25)

Adjusted by age, sex and number of first degree relative with colorectal cancer

Table 6.7 Average direct effects of socioeconomic status indicators on colorectal cancer risk and average mediated effects of any colorectal cancer screening uptake (*medeff* command)

	Multivariable*		Average direct effect		Average mediated effect		Total effect		% of mediated effect	
	OR	**(95% CI)**	**Est**	**95%CI**	**Est**	**95%CI**	**Est**	**95%CI**	**Est**	**95%CI**
Year of schooling	1.00	(0.96, 1.03)	0.0006	(-0.0049, 0.0043)	-0.0011	(-0.0016, -0.0006)	-0.0005	(-0.0062, 0.0035)	18.41	(-666.02, 541.12)
Quintile groups of IRSD	1.02	(0.97, 1.07)	0.0034	(-0.0032, 0.0094)	-0.0015	(-0.0023, -0.0008)	0.0018	(-0.0048, 0.0080)	33.44	(-584.63, 518.32)

Adjusted by age, sex and number of first degree relative with colorectal cancer

Table 6.8 Direct effects of socioeconomic status indicators on the colorectal cancer risk and indirect effect of any colorectal cancer screening uptake (*paramed* command)

	CRC cases		Non-CRC cases		Multivariable*		Natural direct effect		Natural indirect effect		Total effect	
	n	**(%)**	**n**	**(%)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Educational level												
Less than university	610	(71.9)	3,029	(70.8)	1		1		1		1	
University	238	(28.1)	1,249	(29.2)	0.95	(0.80, 1.12)	0.99	(0.83, 1.18)	0.96	(0.94, 0.99)	0.95	(0.80, 1.14)
IRSD group												
Low socioeconomic status (1st–2rd quintile groups)	293	(32.0)	1,563	(34.1)	1		1		1		1	
High socioeconomic status (3rd–5th quintile groups)	624	(68.1)	3,023	(65.9)	1.07	(0.91, 1.25)	1.09	(0.93, 1.28)	0.99	(0.97, 1.00)	1.07	(0.91, 1.27)

Adjusted by age, sex and number of first degree relative with colorectal cancer

Table 6.9 Average direct effects of socioeconomic status indicators on colorectal cancer risk and average mediated effects endoscopy uptake (medeff command)

	Multivariable*		Average direct effect		Average mediated effect		Total effect		% of mediated effect	
	OR	**(95% CI)**	**Est**	**95%CI**	**Est**	**95%CI**	**Est**	**95%CI**	**Est**	**95%CI**
Year of schooling	1.00	(0.96, 1.03)	0.0005	(-0.0049, 0.0042)	-0.0003	(-0.0007, <0.0001)	0.0002	(-0.0055, 0.0041)	-8.49	(-182.06, 164.49)
Quintile groups of IRSD	1.02	(0.97, 1.07)	0.0029	(-0.0037, 0.0090)	-0.0008	(-0.0014, -0.0002)	0.0021	(-0.0046, 0.0084)	-18.60	(-375.35, 210.68)

Adjusted by age, sex and number of first degree relative with colorectal cancer

Table 6.10 Direct effects of socioeconomic status indicators on the colorectal cancer risk and indirect effect of endoscopy uptake (paramed command)

	CRC cases		Non-CRC cases		Multivariable*		Natural direct effect		Natural indirect effect		Total effect	
	n	**(%)**	**n**	**(%)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Educational level												
Less than university	610	(71.9)	3,029	(70.8)	1		1		1		1	
University	238	(28.1)	1,249	(29.2)	0.95	(0.80, 1.12)	0.99	(0.83, 1.18)	0.96	(0.94, 0.99)	0.95	(0.80, 1.14)
IRSD group												
Low socioeconomic status (1st–2rd quintile groups)	293	(32.0)	1,563	(34.1)	1		1		1		1	
High socioeconomic status (3rd–5th quintile groups)	624	(68.1)	3,023	(65.9)	1.07	(0.91, 1.25)	1.08	(0.91, 1.27)	0.99	(0.96, 1.02)	1.06	(0.90, 1.26)

Adjusted by age, sex and number of first degree relative with colorectal cancer

6.3.4. Sensitivity analysis

Figure 6.3 demonstrates sensitivity analyses of the mediated effect of body mass index on the association between socioeconomic status indicators and colorectal cancer risk. For the point estimates of the average mediated effect to be zero, the correlation between error terms of the regression of body mass index and regression of risk of colorectal cancer (ρ) were approximately 0.2. Similarly, Figure 6.4 shows that the ρ-values were 0.1 for the sensitivity analyses of mediated effect of pack-years of smoking on the association between socioeconomic status indicators and colorectal cancer risk. The required four assumptions for causal inference of the mediation analyses were not met fully in these models because the ρ departed from 0. These ρ values indicated that there may be variables omitted in these analytic models, which affects both the mediator and the outcome variables. The *medsens* command does not allow the user to conduct sensitivity analysis on mediated effect of any colorectal cancer screening and endoscopy uptake because the mediator (colorectal cancer screening uptake) and the outcome (colorectal cancer) are both binary.

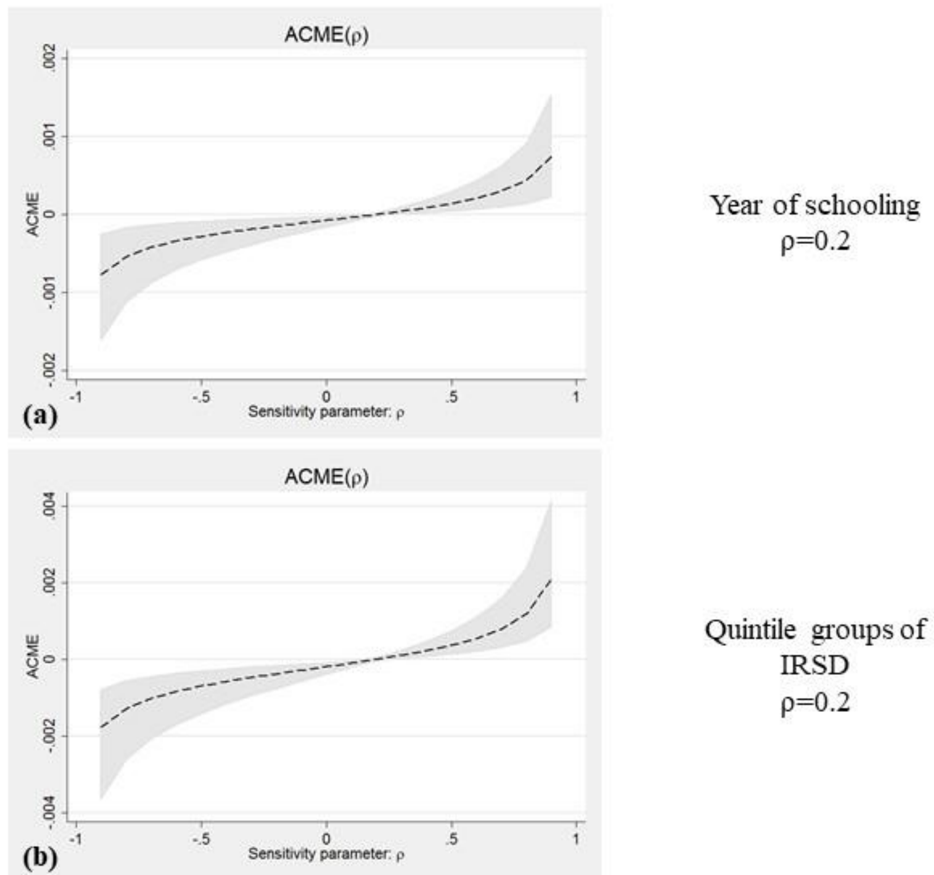


Figure 6.3 Graphical display of sensitivity analyses for mediated effect of body mass index on the association between (a) year of schooling and (b) quintile groups of IRSD and colorectal cancer risk

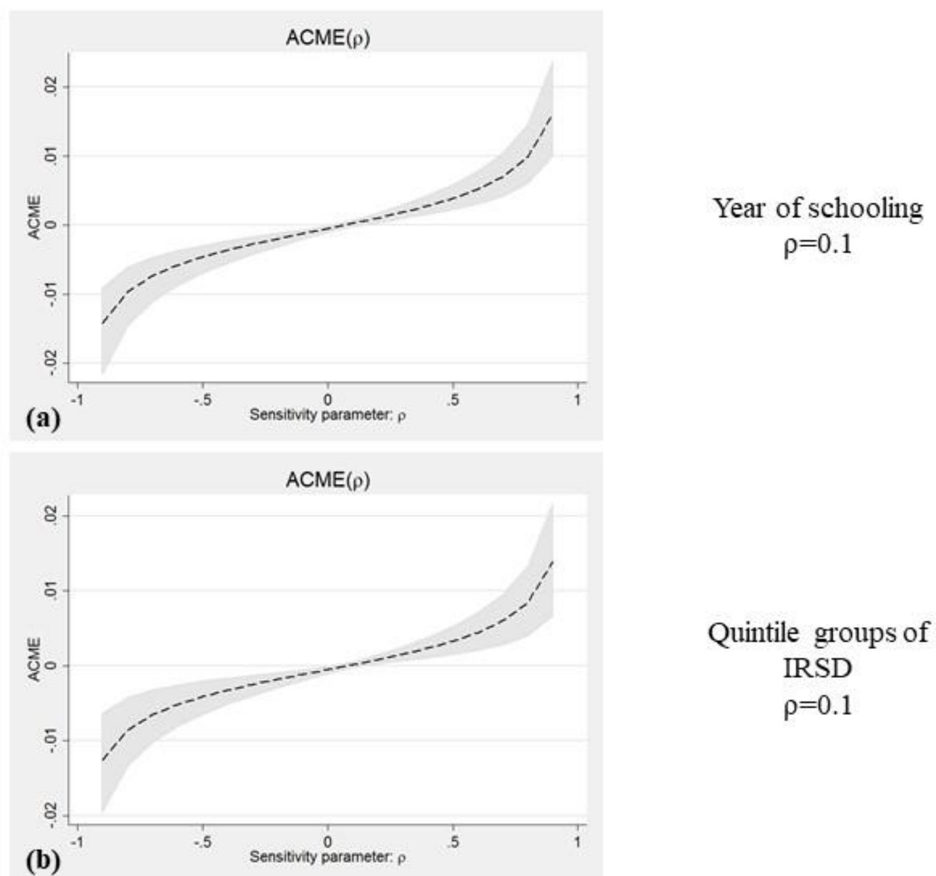


Figure 6.4 Graphical display of sensitivity analyses for mediated effect of pack-years of smoking on the association between (a) year of schooling and (b) quintile groups of IRSD and colorectal cancer risk

6.4. Discussion

In this study, I found no association between socioeconomic status (as assessed by educational attainment and IRSD) and risk of colorectal cancer. In addition, there was no evidence of mediated effect of health behaviours and colorectal cancer screening uptake on the associations.

I found no association between educational attainment and risk of colorectal cancer. Out of five studies[141, 214, 228, 230, 240] which investigated the association between educational attainment and colorectal cancer risk, two were conducted in Europe[230, 240] and reported a non-significant association. An Italian study[228] conducted between 1985-1987 found that higher educational attainment groups had greater risk of colorectal cancer while the other two United States studies[141, 214] reported that lower educational attainment groups had higher risk of colorectal cancer. For the area of residence, I found no association between IRSD and colorectal cancer risk. From 14 articles[141, 213, 216, 217, 220, 221, 224, 232-235, 238, 239, 242] which investigated the association between composite socioeconomic status indicators and risk of colorectal cancer, there was a variety of the results. Five studies which were conducted in the United States[217, 220], Spain[239], Puerto Rico[224] and Japan[242] reported that the higher socioeconomic groups had greater risk of colorectal cancer. In two studies from the United States, only Hispanics showed increased risk of colorectal cancer with increasing composite socioeconomic indicator. In contrast, eight studies which were conducted in the United States[141, 217, 220], Ireland[232, 233], Scotland[234, 235] and Germany[238] found that people with higher composite socioeconomic status indicators had lower risk of colorectal cancer.

The association between socioeconomic status and colorectal cancer risk is complex and varies widely across the world. Different contexts of study design, country of study and source of data play an important role of explaining this heterogeneity. The Australasian Colon Cancer Family Registry participants included in this analysis, were population-based case-control families. Therefore, the proportion of new colorectal cancer cases might be higher compared to the general Australian population. In this analysis, 44.6% and 52.0% of the participants had vocational or university degrees and were living in

higher socioeconomic status areas (4th and 5th quintile groups of IRSD). This skewed population distribution towards higher socioeconomic categories may contribute to the slightly weak socioeconomic disparities on colorectal cancer risk found in this analysis. Not only the higher proportion and homogeneity of higher socioeconomic status groups. Potential confounding factor, not collected by the Australasian Colon Cancer Family Registry might have also prevented the association between socioeconomic status and colorectal cancer risk from being detected.

The magnitude of the association between socioeconomic status indicators and risk of colorectal cancer in this analysis was quite small. I can expect small mediated effect on these association because the mediated effect is relative to the total effect. On the other hand, the opposite direction between direct and indirect effects may contribute to the small magnitude of the total effect.

From my mediation analyses, I could not discern any evidence for a mediated effect of health behaviours (body mass index and obesity) and colorectal cancer screening uptake on the associations between socioeconomic status indicators and colorectal cancer risk. My finding is consistent with a study conducted in Canada(223). However, two studies conducted in the United States(79, 80) reported the mediated effect of health behaviours on the socioeconomic disparities of colorectal cancer risk. Doubeni(79) reported the mediated effect of body mass index and smoking on the association between socioeconomic status (educational attainment and neighbourhood socioeconomic status) and risk of colorectal cancer. Kim(80) also provided evidence of the mediated effect of body mass index on the association between neighbourhood socioeconomic status and both colon and rectal

cancer risks and the mediated effect of smoking on the association between neighbourhood socioeconomic status and risk of rectal cancer

The different degree of the mediated effect of body mass index and pack-year of smoking on the associations between socioeconomic status indicators and risk of colorectal cancer likely came from the differences of statistical methods of mediation analysis, study population and country of study. I used the counterfactual approach which estimated the average mediated effect, whereas others used path analysis which cannot estimate the magnitude of the mediated effect(80); percentage change in socioeconomic coefficient to identify the mediated effect(223); and percentage mediation calculated from difference of coefficient of socioeconomic status between without and with the mediator(79). For the study population, these three studies used the specific study population and dataset from the Nurses' Health study conducted in the United States(80); population-based case-control study conducted in Ontario, Canada(223); and prospective NIH-AARP in the United States(79). These studies were similar to the Australasian Colon Cancer Family Registry in terms of the objective to answer the aetiology of colorectal cancer. However, the number of sample size were different with range of 2,135 to 296,527.

The mediated effect of colorectal cancer screening on the association between socioeconomic status and risk of colorectal cancer should be interpreted with caution. Firstly, overall screening uptake rate for any screening modality (21.9%) and endoscopy (19.5%) were low. Secondly, as mentioned in previous chapters, the Australasian Colon Cancer Family registry is a family-based cohort study. The findings of this analysis might, therefore, not be applicable to the general population.

Mediation analysis based on the counterfactual approach requires the assumption of "no unmeasured confounding factor" that is unlikely for observation studies such as this one. However, the Stata mediation package employs the *medsens* command which is a sensitivity analysis to investigate the assumption of "no unmeasured confounding factor". Moreover, this package has a cluster subcommand which can account for non-independence of relatives in the sample. Therefore, the Stata mediation package consisting of *medeff* and *medsens* commands was adopted for these mediation analyses.

Mediation analysis has increased in popularity with advancing development of analytic techniques. In my analysis, there were a few limitations related to the mediation analysis. Firstly, the single mediator analysis was used in this study to be an overview and simplify the complex causal pathway of the association between socioeconomic status and colorectal cancer risk. Nevertheless, the mediation analysis with multiple mediators will yield a more comprehensive description of the socioeconomic disparities in colorectal cancer risk. Secondly, the proportion of mediated effect is unlikely to be useful in this analysis because the direct and indirect effects had opposite directions. So, my interpretations were based on the indirect effects and the 95% CIs from *medeff* and *paramed* commands.

In sum, no association between socioeconomic status and colorectal cancer risk, or mediated effects of health behaviours and colorectal cancer screening uptake on the socioeconomic disparities of colorectal cancer risk were demonstrated in this study. Nevertheless, the pathways of the socioeconomic disparities and colorectal cancer risk, which are quite complex because of several covariates and mediators, should be

investigated comprehensively in order to establish the most effective health interventions to prevent further morbidity and mortality from colorectal cancer.

Chapter 7. Discussion and Conclusion

7.1. Summary of my study

The four aims of this thesis were to: (a) estimate the association between socioeconomic status and colorectal cancer screening uptake, (b) estimate the association between socioeconomic status and risk of colorectal cancer, (c) identify mediators of the association between socioeconomic status and colorectal cancer screening uptake and (d) identify mediators of the association between socioeconomic status and risk of colorectal cancer.

For the first aim, I conducted a systematic review and meta-analysis of 31 studies to estimate the association between socioeconomic status and colorectal cancer screening uptake. My analysis showed that, on average, people in the highest educational attainment group were 43% more likely to participate in colorectal cancer screening than those in the lowest educational attainment group. Similarly, the odds of screening uptake (with any procedure) were 32% higher for people in the highest income group than those in the lowest income group. The positive associations between higher educational attainment, higher income level and screening uptake were particularly strong for FOBT and endoscopy. For two socioeconomic status indicators (educational attainment and income) investigated, the meta-analyses showed moderate to high heterogeneity between studies, which were partially explained by the year of data collection and country in which the study was conducted. The studies in the meta-analyses showed socioeconomic disparities of colorectal cancer screening uptake worldwide. The greatest disparities were

consistently reported in studies conducted in the United States and there was less heterogeneity in these studies.

For the second aim, I conducted a systematic review and meta-analyses to estimate the association between socioeconomic status and risk of colorectal cancer. I showed that the risk of colon cancer and colorectal cancer were 9% and 18% respectively higher for people living in the most deprived area than for those living in the least deprived area. In the studies conducted in North America, the lowest educational attainment group had the highest risk of colorectal cancer, while in the other studies, the highest educational attainment group had the highest risk of colorectal cancer. Heterogeneity between studies was partially explained by continent of study and study design. Studies conducted in North America showed the most consistent results, demonstrating the highest risk of colorectal cancer in people with the lowest socioeconomic status. Overall, my analyses showed that, globally, people in lower socioeconomic groups are at a greater risk of colorectal cancer than those in higher socioeconomic groups, despite some geographic differences in the association between educational attainment and colorectal cancer risk.

For the third aim, I used data from the Australasian Colon Cancer Family Registry to identify mediators of the association between socioeconomic status and colorectal cancer screening uptake. I showed that the probability of colorectal cancer screening increased by 9% and 9% respectively for each additional year of schooling and each increasing in quintile group of IRSD. Moreover, 13.7% of the association between years of schooling and colorectal cancer screening uptake and 15.5% of the association between IRSD quintile groups and screening uptake were mediated via pack-years of smoking. These findings suggest the existence of socioeconomic disparities in colorectal cancer screening

uptake in Australia and provide evidence of an indirect or mediated effect from socioeconomic status to colorectal cancer screening uptake via smoking.

For the fourth aim, I identified and evaluated the effect of mediators on the association between socioeconomic status and risk of colorectal cancer. There was no evidence of the association between socioeconomic status indicators (educational attainment and area of residence) and risk of colorectal cancer. There was no evidence of marginal mediated effects of health behaviours (body mass index and pack-years of smoking) and colorectal cancer screening uptake on the association between socioeconomic status and risk of colorectal cancer were demonstrated. These results show no evidence of socioeconomic disparities on risk of colorectal cancer and no mediated effect of health behaviours and colorectal cancer screening uptake on socioeconomic disparities of colorectal cancer.

I have shown that socioeconomic disparities in colorectal cancer risk and screening uptake generally persist globally. The extent of these disparities depends on the country in which the studies were conducted but it was particularly present in studies conducted in the United States for the screening uptake and in North America for colorectal cancer risk. The socioeconomic disparities in colorectal cancer risk and screening uptake persist, even in Australia where the population is covered by a universal healthcare system.

7.2. Importance of my study

That socioeconomic factors have an important impact on colorectal cancer screening uptake was well known before I began this research. This topic has been studied and confirmed by researchers worldwide in several systematic reviews that have been updated frequently. My research contributes the important insight into lower socioeconomic

groups that had lower screening uptake regardless of which screening modality was offered, which socioeconomic status indicator was used or where the study was conducted. The social gradient in screening uptake persists despite the heterogeneity in screening programs, uptake rates and year of data.

Most of the studies investigating the association between socioeconomic status and colorectal cancer screening uptake have attempted to adjust for possible confounders. They may, however, have controlled for a mediator (such as accessibility to healthcare or risky health behaviours) that is caused by socioeconomic status and affects colorectal cancer screening uptake. This is over-adjusting because the mediator is in the causal pathway and its inclusion will result in a biased estimate of the association.

What my research has added to the understanding of the impact of socioeconomic status on colorectal cancer risk is that this problem depends on the specific country and how socioeconomic status is measured. In North America, people in lower educational attainment groups had a higher risk of colorectal cancer. In contrast, people in the higher educational attainment groups in European countries had higher risk of colorectal cancer than people in lower educational attainment groups. People who lived in the most deprived areas in the North American studies had a slightly lower risk of colorectal cancer than people in the less deprived areas. People who lived in the most deprived areas in the other studies had a greater risk of colorectal cancer than people in the less deprived areas. Overall, people in the lower income groups had increased risk of colorectal, colon and rectal cancers worldwide. Similar to the findings on socioeconomic disparities in colorectal cancer screening uptake, most studies of the association between socioeconomic status and risk of colorectal cancer were adjusted for several potential

confounders including health behaviours and colorectal cancer screening uptake. Therefore, as for colorectal cancer screening uptake, the magnitude of socioeconomic disparities in colorectal cancer risk is likely to be biased.

I conducted a mediation analysis to identify and evaluate the factors that cause these association, using data from a large Australian study of 2,193 participants for the outcome of colorectal cancer screening uptake and 5,753 participants for the outcome of risk of colorectal cancer. I focused on just two indicators of socioeconomic status: a measure of deprivation based on the participants' area of residence and a personal measure of educational attainment based on a questionnaire. I investigated two potential mediators that were chosen to be markers of unhealthy behaviour: obesity and smoking, both ascertained using a questionnaire. Colorectal cancer screening uptake also was examined as a potential mediator for the outcome of risk of colorectal cancer. I focused my research on a single country, Australia, which has had the highest age-standardised incidence rate of colon and rectal cancers and has a national bowel cancer screening program that suffers from poor participation.

7.3. My findings and the burden of colorectal cancer in Australia

My findings confirmed the persistence of socioeconomic disparities in colorectal cancer, especially for screening uptake in Australia. Australia has had a national bowel cancer screening program since 2006, but the incidence of colon and rectal cancers continues to be among the highest in the world. After nearly 15 years since the start of the national bowel cancer screening program, people in the lower socioeconomic groups continue to have lower screening uptake, higher incidence of colorectal cancer and higher mortality rate from colorectal cancer. Health interventions targeting the most deprived

socioeconomic groups should be implemented to prevent colorectal cancer mortality through early detection. Moreover, the indirect pathways from socioeconomic status to colorectal cancer via health behaviour factors such as obesity and smoking found in my study suggest possible areas of interest for interventions to reduce the socioeconomic disparities in colorectal cancer. For example, health promotion campaigns to improve screening among smokers could be implemented. Interventions targeting unhealthy behaviours might reduce the disease burden of other chronic conditions such as heart disease, metabolic syndromes and other cancers.

7.4. Strengths and limitations

There were several main strengths of my thesis that combined to show a comprehensive picture of socioeconomic disparities in colorectal cancer. Firstly, I was able to demonstrate the existence of socioeconomic disparities in colorectal cancer worldwide and in the pooled estimates from a meta-analysis of international studies. Generally, there was high heterogeneity between studies, as I had expected, but subgroup analyses by socioeconomic indicator, screening modality, cancer site and geographic location of studies reduced the heterogeneity to low or no heterogeneity in several pooled estimates. Therefore, the pooled estimates represent a good average of the association. Moreover, the meta-analysis confirmed that the magnitudes of socioeconomic disparities in risk of colorectal cancer were different depending on the geographical location of the studies.

Secondly, the strong impact of confounders in observational studies is taken into account by mediation analysis based on the counterfactual approach. Causal inference in the counterfactual approach takes certain assumptions into account, including that of no confounders. For my mediation analyses, which were based on an observational study,

the issue of confounding is unavoidable. However, mediation analysis based on the counterfactual approach includes the impact of sensitivity analysis to calculate the strength of the assumptions. Therefore, the impact of confounding on the results was considered and quantified in this thesis.

Lastly, my use of directed acyclic graphs illustrated the complexity of the association between socioeconomic status and colorectal cancer outcomes. These causal diagrams help to identify confounding factors and mediators of the association. They demonstrate the relationship between covariates and give a picture the potential consequences of controlling for those covariates.

The analyses presented in my thesis have some limitations that need to be considered for the potential translation of my findings into public health policy. Firstly, there are several causal pathways and mediators that explain the socioeconomic disparities in colorectal cancer risk and screening uptake. In this thesis, a single mediator model was used that partially captures the complex causal pathway. Nevertheless, my findings provided evidence of how obesity and smoking mediate the association between socioeconomic status and colorectal cancer screening uptake and risk. These are a good starting point for more advanced analyses to confirm the association.

Secondly, the magnitude of the mediated effects of health behaviours on the association between socioeconomic status and risk of colorectal cancer cannot be quantified completely because of the opposite direction of the direct and indirect effects. The mediated or indirect effects of health behaviours on the association between socioeconomic status and colorectal cancer risk and screening uptake were small and were likely to be caused by the marginal total effect of the association. Nevertheless, I

found evidence of mediated effects of health behaviour on the association between socioeconomic status on colorectal cancer screening uptake and risk.

Lastly, the mediation analysis needs the large sample size and strong association between exposure and outcome to demonstrate the effect of the mediator. This analysis might not sensitive enough to detect the small prevalence and weak association especially in the complicated causal pathway.

7.5. Recommendations for further studies

Further research is needed on this topic. I propose that comprehensive socioeconomic status indicators and large prospective cohort studies on colorectal cancer are essential to generate effective interventions to minimise socioeconomic disparities in colorectal cancer. Each socioeconomic indicator has its own meaning and represents a different aspect of social and economic factors. IRSD is one of the composite socioeconomic status indicators that is currently used in Australia, but the main limitation of IRSD is ecological fallacy. Therefore, a comprehensive socioeconomic status indicator that represents individual socioeconomic status should be established.

Cancer is a rare outcome with multifactorial origins, but it causes a huge burden for affected people and the national health budget. A prospective cohort study that collects all covariates related to colorectal cancer, is required to understand the complex causal pathway of colorectal cancer. The complete causal pathway will be useful to develop precise public health interventions, while a life course approach will be helpful to investigate the socioeconomic gradient in population health.

Several advanced approaches will improve the validity of the mediation analysis. The multiple mediator and simulation models offer a more complete description of the covariates of the association. Generally, causal pathways between socioeconomic status and colorectal cancer risk and screening uptake are complex. Investigating several mediators simultaneously with the complete set of confounding factors will identify the direct and indirect effects via mediators of the socioeconomic disparities in colorectal cancer. Simulation analysis is the option for these approaches because it imputes missing data and is based on large datasets that can be linked to other sources of data, such as census or cancer registry data.

7.6. Conclusion

Socioeconomic disparities in colorectal cancer are persisting globally and in Australia. I found evidence of the mediated effect of health behaviours on the association between socioeconomic status and colorectal cancer risk and screening uptake by using the counterfactual approach. Advances in mediation analysis such as multiple mediator models and simulation studies, will enable more comprehensive analyses of the socioeconomic disparities in colorectal cancer.

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Appendices

Appendix A: Chapter 3 Socioeconomic Status and Colorectal Cancer Screening Practices: A Systematic Review and Meta-analysis

Appendix A table 1 Characteristics of the studies which measured effect of educational attainment on colorectal cancer screening uptake

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity#	Screening modality	Reporting methods	Education level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
López-Charneco, 2013[196]	Puerto Rico	2,920	Combined	≥50	Non-specific	Any screening test	Self-report	>High school/ <high school	1.52	(1.25, 1.89)	• Age • Sex • Marital status • Employment status • Healthcare coverage • Perceived general health status • Routine check-up past year • Current smoking status
Hall, 2012[175]	United States	204	Male	≥50	African Americans	Any screening test	Self-report	Graduate/ high school/general equivalence diploma	2.16	(0.79, 5.92)	• Age • Family history of colorectal cancer • Insurance status
Hall, 2012[175]	United States	135	Male	≥50	Caucasians	Any screening test	Self-report	Graduate/ high school/general equivalence diploma	2.02	(0.58, 7.06)	• Age • Family history of colorectal cancer • Insurance status
Greene, 2012[173]	United States	2,092	Combined	≥50	Non-specific	Any screening test	Self-report	≥High school/ <high school	0.99	(0.53, 1.87)	• Age • Sex • Marital status • Annual income • Race • Employment status • Has a healthcare provider • ≥5 visits by health personnel in past year • Healthcare provider explains things in an understandable way • Received any screening advice

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity[#]	Screening modality	Reporting methods	Education level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Walsh, 2009[188]	United States	808	Combined	50–79	Vietnamese	Any screening test	Self-report	≥13 years/ ≤6 years	1.01	(0.60, 1.71)	• Age • Sex • Marital status • Years in United States • Employment • Self-rated health • Perceived risk of developing cancer • Ever heard of polyp • Colorectal cancer knowledge • Provider gender • Gender concordance • Ethnicity concordance • Language concordance
Shih, 2008[186]	United States	12,179	Combined	≥50	Non-specific	Any screening test	Self-report	≥College/ <high school	2.04	(1.77, 2.36)	• Age • Sex • Marital status • Income level • Race/ethnicity • Access barrier • Self-perceived health status • Previous history of care • Census region • Metropolitan Statistical Areas status
Ananthakrishnan, 2007[169]	United States	596,470	Combined	≥65	Non-specific	Any screening test	Medicare record	≥High school/ <high school	1.52	(1.48, 1.55)	• Age group • Sex • Income level • Significant interaction

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity#	Screening modality	Reporting methods	Education level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Ata, 2006[170]	United States	12,498	Combined	≥50	Non-specific	Any screening test	Self-report	Post-graduate/ <high school	2.08	(1.67, 2.58)	• Age • Sex • Marital status • Annual family income • Race • Region • Metropolitan Statistical Areas size • Health insurance • A usual plan of healthcare • Time since last doctor visit • Family cancer history • History of other cancer • Perceived health status • Smoking status • Body mass index • Exercise
Maxwell, 2000[178]	United States	218	Female	≥50	Filipino migrants	Any screening test	Self-report	Some college/ <high school	0.85	(0.36, 2.00)	• Age • % lifetime in United States • Marital status • Health insurance • Employment • Ever had a check up
Maxwell, 2000[178]	United States	229	Female	≥50	Korean migrants	Any screening test	Self-report	Some college/ <high school	0.86	(0.38, 2.02)	• Age • % lifetime in United States • Marital status • Health insurance • Employment • Ever had a check up

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity#	Screening modality	Reporting methods	Education level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Halbert, 2016[174]	United States	262	Combined	50–75	African Americans	Endoscopy	Self-report	>High school/ ≤ high school	1.26	(0.65, 2.45)	• Age • Sex • Marital status • Income level • Employment status • Health insurance • Usual source of medical care • Healthcare provider communication about screening • Self-efficacy for screening • Present temporal orientation • Neighbourhood satisfaction
López-Charneco, 2013*[196]	Puerto Rico	2,920	Combined	≥50	Non-specific	Endoscopy	Self-report	> High school/ <high school	2.56	(2.08, 3.23)	• Age • Sex • Marital status • Employment status • Healthcare coverage • Perceived general health status • Routine check-up past year • Current smoking status
Patel, 2012[183]	United States	460	Combined	≥50	African Americans	Endoscopy	Self-report	> High school/ <high school	2.47	(1.25, 4.86)	• Age • Sex • Marital status • Annual household income • City • Medical visit in past 12 months • Family history of cancer • Employment status • Health insurance • Body mass index • Smoking status • Self-rate health status • At least one alcoholic beverage in the past 30 days

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity#	Screening modality	Reporting methods	Education level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Hall, 2012*[175]	United States	204	Male	≥50	African Americans	Endoscopy	Self-report	Graduate/ high school/general equivalence diploma	1.32	(0.49, 3.54)	• Age • Family history of colorectal cancer • Insurance status
Hall, 2012*[175]	United States	135	Male	≥50	Caucasians	Endoscopy	Self-report	Graduate/ high school/general equivalence diploma	1.64	(0.55, 4.90)	• Age • Family history of colorectal cancer • Insurance status
Richard, 2011[184]	United States	18,358	Combined	≥50	Non-specific	Endoscopy	Self-report	College graduate/ high school	1.12	(1.01, 1.23)	• Age • Sex • Insurance • Place of birth • Poverty level • Neighbourhood income
Adams-Campbell, 2010[168]	United States	6,836	Female	50–59	African Americans	Endoscopy	Self-report	≥16 years/ ≤12 years	1.30	(1.13, 1.48)	• Marital status • Region • Body mass index • Current hormone use • Health insurance • Alcohol use • Smoking status • Mammography • Strenuous physical activity
Adams-Campbell, 2010[168]	United States	2,757	Female	≥60	African Americans	Endoscopy	Self-report	≥16 years/ ≤12 years	1.09	(0.87, 1.36)	• Marital status • Region • Body mass index • Current hormone use • Health insurance • Alcohol use • Smoking status • Mammography • Strenuous physical activity

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity#	Screening modality	Reporting methods	Education level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Doubeni, 2009[171]	United States	8,355	Combined	65–80	Non-specific	Endoscopy	Medicare record	> High school/ <high school	1.82	(1.30, 2.50)	• Age • Sex • Marital status • Household income level • Usual place of healthcare • Delayed care due to cost • Language of the interview • Residence in a Metropolitan Statistical Areas • Race-ethnicity • Insurance type • Self-reported general health status • History of non–skin cancers.
Doubeni, 2009[171]	United States	7,646	Combined	65–80	Non-specific	Endoscopy	Medicare record	> High school/ <high school	1.52	(1.02, 2.27)	• Age • Sex • Marital status • Household income level • Usual place of healthcare • Delayed care due to cost • Language of the interview • Residence in a Metropolitan Statistical Areas • Race-ethnicity • Insurance type • Self-reported general health status • History of non–skin cancers.

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity[#]	Screening modality	Reporting methods	Education level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Walsh, 2009*[188]	United States	808	Combined	50–79	Vietnamese	Endoscopy	Self-report	≥13 years/ ≤6 years	0.82	(0.52, 1.30)	• Age • Sex • Marital status • Years in United States. • Employment • Self-rated health • Perceived risk of developing cancer • Ever heard of polyp • CRC knowledge • Provider gender • Gender, ethnicity, and language concordance
Maxwell, 2008[179]	United States	487	Combined	50–75	Filipino American migrants	Endoscopy	Self-report	≥ College/ <college	1.06	(0.59, 1.89)	• Age • Sex • Marital status • Annual income • % lifetime in United States • Language of interview • Has health insurance • Has regular doctor
Ananthakrishnan, 2007*[169]	United State	596,470	Combined	≥65	Non-specific	Endoscopy	Medicare record	> High school/ <high school	1.36	(1.31, 1.40)	• Age group • Sex • Income level • Significant interaction

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity#	Screening modality	Reporting methods	Education level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Gorin, 2005[172]	United States	234	Combined	≥40	Latinos	Endoscopy	Self-report	≥Bachelor's degree/ ≤ grade 12	2.75	(1.62, 4.66)	• Age • Sex • Marital status • Ethnicity • Smoking status • Personal history of cancer • Acculturation • Health insurance coverage • Visited a primary healthcare provider over the past 12 months • Self-rated health status • Used at least one other cancer screening test
Solmi, 2015[197]	United Kingdom	1,833	Combined	61–69	Non-specific	FOBT	Self-report	Degree or higher/ no qualification	1.06	(0.98, 1.15)	• Age • Sex • Marital status • Ethnicity • Number of people in household • Self-reported general health • Long-standing limiting illness • Health literacy • Partner who screened • Net non-pension wealth • Occupational class • Vehicles • Housing tenure • Economic activity • Government Office Region
Kobayashi, 2014[195]	United Kingdom	3,078	Combined	60–75	Non-specific	FOBT	Self-report	Degree or equivalent/ no qualification	1.10	(0.87, 1.40)	• Age • Sex • Health literacy • Net non-pension wealth

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity#	Screening modality	Reporting methods	Education level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
López-Charneco, 2013*[196]	Puerto Rico	2,920	Combined	≥50	Non-specific	FOBT	Self-report	>High school/ <high school	1.27	(1.01, 1.96)	• Age • Sex • Marital status • Employment status • Healthcare coverage • Perceived general health status • Routine check-up past year • Current smoking status
Hall, 2012*[175]	United States	204	Male	≥50	African Americans	FOBT	Self-report	Graduate/ high school or general equivalence diploma	1.41	(0.57, 3.55)	• Age • Family history of colorectal cancer • Insurance status
Hall, 2012*[175]	United States	135	Male	≥50	Caucasians	FOBT	Self-report	Graduate/ high school or general equivalence diploma	1.02	(0.36, 2.80)	• Age • Family history of colorectal cancer • Insurance status
Frederiksen, 2010[194]	Denmark	173,670	Combined	50–74	Non-specific	FOBT	Project record	>12 years/ ≤7 years	1.38	(1.33, 1.43)	• Age • Sex • Income level • County • Ethnicity • Cohabitation • Employment
Dimitrakaki, 2009[193]	Greece	552	Female	50–69	Non-specific	FOBT	Self-report	High/ low	3.43	(0.13, 93.84)	• Age • Marital status • Region • Smoking • General health • Social class • Insurance

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity#	Screening modality	Reporting methods	Education level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Dimitrakaki, 2009[193]	Greece	483	Male	50–69	Non-specific	FOBT	Self-report	High/ low	0.60	(0.05, 7.18)	• Age • Marital status • Region • Smoking • General health • Social class • Insurance
Doubeni, 2009[171]	United States	8,355	Combined	65–80	Non-specific	FOBT	Medicare	>High school/ <high school	1.75	(1.04, 3.03)	• Age • Sex • Marital status • Household income • Usual place of healthcare • Delayed care due to cost • Language of the interview • Residence in a Metropolitan Statistical Areas • Race-ethnicity • Insurance type • Self-reported general health status • History of non–skin cancers.
Doubeni, 2009[171]	United States	7,646	Combined	65–80	Non-specific	FOBT	Medicare	>High school/ <high school	1.72	(1.01, 2.94)	• Age • Sex • Marital status • Household income • Usual place of healthcare • Delayed care due to cost • Language of the interview • Residence in a Metropolitan Statistical Areas • Race-ethnicity • Insurance type • Self-reported general health status • History of non–skin cancers.

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity[#]	Screening modality	Reporting methods	Education level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Walsh, 2009*[188]	United States	808	Combined	50–79	Vietnamese	FOBT	Self-report	≥13 years/ ≤6 years	1.13	(0.72, 1.77)	• Age • Sex • Marital status • Years in U.S. • Employment • Self-rated health • Perceived risk of developing cancer • Ever heard of polyp • CRC knowledge • Provider gender • Gender concordance • Ethnicity concordance • Language concordance
Maxwell, 2008[179]	United States	487	Combined	50–75	Filipino American migrants	FOBT	Self-report	≥College/ <college	1.08	(0.58, 2.01)	• Age • Sex • Marital status • Annual income • % lifetime in United States • Language of interview • Has health insurance • Has regular doctor
Gorin, 2005[172]	United States	234	Combined	≥40	Latinos	FOBT	Self-report	≥ Bachelor's degree/ ≤ grade 12	1.78	(0.86, 3.67)	• Age • Sex • Marital status • Ethnicity • Smoking status • Personal history of cancer • Acculturation • Health insurance coverage • Visited a primary healthcare provider over the past 12 months • Self-rated health status • Used at least one other cancer screening test

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity#	Screening modality	Reporting methods	Education level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Kim, 1998[176]	United States	263	Combined	40–69	Korean Americans	FOBT	Self-report	>12 years/ ≤12 years	0.80	(0.30, 2.15)	• Age • Sex • Usual source of healthcare • Knowledge of cancer warning signals • Length of residence in United States
Meyer, 2016[181]	United States	57,002	Combined	60–64, 66–70	Non-specific	US Preventive Services Task Force guideline	Self-report	≥College/ <high school	1.56	(1.35, 1.80)	• Medicare eligibility • Annual household income • Residence location • Access to a regular healthcare provider
Oluyemi, 2014[182]	United States	155,020	Combined	50–75	Non-specific	US Preventive Services Task Force guideline	Self-report	Graduated college/ <high school	1.75	(1.59, 1.92)	• Age • Sex • Annual income level • Race • Body mass index • Health insurance • Diabetes • Smoking
Oluyemi, 2014[182]	United States	197,969	Combined	50–75	Non-specific	US Preventive Services Task Force guideline	Self-report	Graduated college/ <high school	1.64	(1.49, 1.82)	• Age • Sex • Annual income level • Race • Body mass index • Health insurance • Diabetes • Smoking

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity#	Screening modality	Reporting methods	Education level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Oluyemi, 2014[182]	United States	229,202	Combined	50–75	Non-specific	US Preventive Services Task Force guideline	Self-report	Graduated college/ <high school	1.85	(1.72, 2.00)	• Age • Sex • Annual income level • Race • Body mass index • Health insurance • Diabetes • Smoking
Liss, 2014[177]	United States	226,546	Combined	50–75	Non-specific	US Preventive Services Task Force guideline	Self-report	College graduate/ <high school	1.27	(1.22, 1.30)	• Age • Sex • Income level • Race • Region • Insurance • Usual care • Check-up in past year
Ryu, 2014[185]	United States & South Korea	519	Combined	≥50	Korean Americans	US Preventive Services Task Force guideline	Self-report	≥ High school/ <high school	0.87	(0.21, 3.69)	• Age • Sex • Marital status • Income level • Urban versus rural place of residence • Health insurance status • English proficiency
Ryu, 2014[185]	United States & South Korea	3,532	Combined	≥50	Caucasians	Guideline	Self-report	≥ High school/ <high school	1.16	(0.92, 1.47)	• Age • Sex • Marital status • Income level • Urban versus rural place of residence • Private health insurance status
Ouakrim, 2012[189]	Australia	1,627	Combined	≥18	Non-specific	Guideline	Self-report	≥Tertiary school/ <tertiary school	2.72	(1.65, 4.48)	• Age (parsimonious model)

#Race/ ethnicity categories as reported in the publication

*were not included in the meta-analysis

Appendix A table 2 Characteristics of the studies which measured effect of income in colorectal cancer screening uptake

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity#	Screening modality	Reporting methods	Income level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Greene, 2012[173]	United States	2,092	Combined	≥50	Non-specific	Any screening test	Self-report	Household: >$15,000/ ≤$15,000	1.56	(0.85, 2.86)	• Age • Sex • Marital status • Education level • Race • Employment status • Has a healthcare provider • ≥5 visits with healthcare provider in past year • Healthcare provider explains things in an understandable way • Received any screening advice
Shih, 2008[186]	United States	12,179	Combined	≥50	Non-specific	Any screening test	Self-report	Poverty level: ≥500% (very rich)/ <200% (very poor)	1.33	(1.15, 1.54)	• Age • Sex • Marital status • Education level • Race/ethnicity • Access barrier • Self-perceived health status • Previous history of care • Census region • Metropolitan Statistical Areas status

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity[#]	Screening modality	Reporting methods	Income level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Ata, 2006[170]	United States	12,498	Combined	≥50	Non-specific	Any screening test	Self-report	Household: ≥$65,000/ <$20,000	1.28	(1.04, 1.58)	• Age • Sex • Marital status • Race • Region • Metropolitan Statistical Areas size • Health insurance • A usual plan of healthcare • Time since last doctor visit • Family cancer history • History of other cancer • Perceived health status • Smoking status • Body mass index • Exercise • Education
Halbert, 2016[174]	United States	262	Combined	50–75	African Americans	Endoscopy	Self-report	Area of living: >$20,000/ ≤$20,000	2.09	(1.07, 4.06)	• Age • Sex • Marital status • Education level • Employment status • Health insurance • Usual source of medical care, • Healthcare provider communication about screening • Self-efficacy for screening • Present temporal orientation • Neighbourhood satisfaction

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity#	Screening modality	Reporting methods	Income level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Menon, 2014(180)	United States	275	Combined	≥50	South Asians	Endoscopy	Self-report	Individual: >$15,000/ <$15000	2.70	(1.02, 7.13)	• Age • Marital status • Education level • Birthplace • Religious affiliation • Years spent in United States • Employment • Health insurance • Whether he/she had a regular doctor • Whether the doctors were members of their community • Family history of cancer • Acculturation-language
Richard, 2011(184)	United States	18,356	Combined	≥50	Non-specific	Endoscopy	Self-report	Area of living: highest income/ lowest income	1.12	(1.03, 1.22)	• Age • Sex • Education level • Place of birth • Insurance • Poverty level
Richard, 2011*(184)	United States	18,356	Combined	≥50	Non-specific	Endoscopy	Self-report	Poverty level: ≥600% (very rich)/ <100% (very poor)	1.27	(1.26, 1.29)	• Age • Sex • Education level • Place of birth • Insurance • Neighbourhood income

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity#	Screening modality	Reporting methods	Income level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Doubeni, 2009[171]	United States	8,355	Combined	65–80	Non-specific	Endoscopy	Medicare record	Household: ≥$25,000/ <$25,000	1.47	(1.19, 1.82)	• Age • Sex • Marital status • Education level • Usual place of healthcare • Delayed care due to cost • Language of the interview • Residence in a Metropolitan Statistical Areas • Race-ethnicity • Insurance type • Self-reported general health status • History of non–skin cancers
Doubeni, 2009[171]	United States	7,646	Combined	65–80	Non-specific	Endoscopy	Medicare record	Household: ≥$25,000/ <$25,000	1.35	(1.05, 1.72)	• Age • Sex • Marital status • Education level • Usual place of healthcare • Delayed care due to cost • Language of the interview • Residence in a Metropolitan Statistical Areas • Race-ethnicity • Insurance type • Self-reported general health status • History of non–skin cancers
Maxwell, 2008[179]	United States	487	Combined	50–75	Filipino American migrants	Endoscopy	Self-report	Individual: ≥$50,000/ <$20,000	3.75	(1.80, 7.82)	• Age • Sex • Marital status • Education level • % lifetime in United States • Language of interview • Has health insurance • Has regular doctor

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity[#]	Screening modality	Reporting methods	Income level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Vlahov, 2005[187]	United States	5,595	Combined	≥50	Non-specific	Endoscopy	Self-report	Household: ≥$100,000/ <$15,000	2.04	(1.61, 2.63)	• Age • Sex • Race/ethnicity • Any insurance • Ever smoked cigarettes • Cancer in immediate family • Body mass index
Frederiksen, 2010[194]	Denmark	173,670	Combined	50–74	Non-specific	FOBT	Self-report	Household: 75–100%/ 1%–24%	1.94	(1.87, 2.01)	• Age • Sex • Education level • County • Ethnicity • Cohabitation • Employment
Doubeni, 2009[171]	United States	8,355	Combined	65–80	Non-specific	FOBT	Medicare record	Household: ≥$25,000/ <$25,000	1.49	(1.19, 2.22)	• Age • Sex • Marital status • Education level • Usual place of healthcare • Delayed care due to cost • Language of the interview • Residence in a Metropolitan Statistical Areas • Race-ethnicity • Insurance type • Self-reported general health status • History of non–skin cancers

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity#	Screening modality	Reporting methods	Income level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Doubeni, 2009[171]	United States	7,646	Combined	65–80	Non-specific	FOBT	Medicare record	Household: ≥$25,000/ <$25,000	0.96	(0.64, 1.45)	• Age • Sex • Marital status • Education level • Usual place of healthcare • Delayed care due to cost • Language of the interview • Residence in a Metropolitan Statistical Areas • Race-ethnicity • Insurance type • Self-reported general health status • History of non–skin cancers
Maxwell, 2008[179]	United States	487	Combined	50–75	Filipino American migrants	FOBT	Self-report	Individual: ≥$50,000/ <$20,000	1.25	(0.53, 2.91)	• Age • Sex • Marital status • Education level • % lifetime in United States • Language of interview • Has health insurance • Has regular doctor
Meyer, 2016[181]	United States	57,002	Combined	60–64, 66–70	Non-specific	US Preventive Services Task Force guideline	Self-report	Household: ≥$25,000/ <$25,000	1.49	(1.36, 1.62)	• Medicare eligibility • Education level • Residence location • Access to a regular healthcare provider
Oluyemi, 2014[182]	United States	155,020	Combined	50–75	Non-specific	US Preventive Services Task Force guideline	Self-report	Individual: ≥$50,000/ <$25,000	1.61	(1.49, 1.72)	• Age • Sex • Marital status • Education level • Body mass index • Race • Health insurance • Diabetes • Smoking

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity#	Screening modality	Reporting methods	Income level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Oluyemi, 2014[182]	United States	197,969	Combined	50–75	Non-specific	US Preventive Services Task Force guideline	Self-report	Individual: ≥$50,000/ <$25,000	1.69	(1.59, 1.82)	• Age • Sex • Marital status • Education level • Body mass index • Race • Health insurance • Diabetes • Smoking
Oluyemi, 2014[182]	United States	229,202	Combined	50–75	Non-specific	US Preventive Services Task Force guideline	Self-report	Individual: ≥$50,000/ <$25,000	1.69	(1.61, 1.82)	• Age • Sex • Marital status • Education level • Body mass index • Race • Health insurance • Diabetes • Smoking
Liss, 2014[177]	United States	226,546	Combined	50–75	Non-specific	US Preventive Services Task Force guideline	Self-report	Household: ≥$75,000/ <$20,000	1.22	(1.19, 1.25)	• Age • Sex • Education level • Race • Region • Insurance • Usual care • Check-up in past year
Ryu, 2014[185]	United States	519	Combined	≥50	Korean Americans	US Preventive Services Task Force guideline	Self-report	Household: 3rd Tertile/ 1st Tertile	1.21	(0.33, 4.44)	• Age • Sex • Marital status • Education level • Urban versus rural place of residence • Health insurance status • English proficiency

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Race/ ethnicity[#]	Screening modality	Reporting methods	Income level (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Ryu, 2014[185]	South Korea	3,532	Combined	≥50	Caucasians	Guideline	Self-report	Household: 3rd Tertile/ 1st Tertile	1.34	(1.08, 1.66)	• Age • Sex • Marital status • Education level • Urban versus rural place of residence • Private health insurance status

[#]Race/ ethnicity categories as reported in the publication

*were not included in the meta-analysis

Appendix A table 3 Characteristics of the studies which measured effect of composite indicators based on area of residence in colorectal cancer screening uptake

Author, year	Country of participants recruitment	N	Sex-specific analyses	Target age group	Screening modality	Reporting methods	Variable	Composite indicators (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Wilf-Miron, 2011[191]	Israel	303,330	Combined	51–74	Any screening test	Medical record	Socioeconomic rank	SER 11–20 (high SES)/ SER 1–10 (low SES)	1.30	(1.27, 1.32)	• Age • Sex • Race (Arab) • Immigration • Ownership of voluntarily supplement health insurance
Pornet, 2010[190]	France	8,691	Combined	50–74	Any screening test	Medical record	Townsend index	1st Quintile (least deprived)/ 5th Quintile (most deprived)	1.47	(1.27, 1.69)	• Age • Sex • Insurance coverage
Doubeni, 2012[167]	United States	100,566	Combined	50–74	Endoscopy	Medicare record	Neighbourhood socioeconomic status	4th Quartile (high SES)/ 1st Quartile (low SES)	1.43	(1.33, 1.54)	• Age • Sex • Modified Charlson comorbidity index at baseline • Number of years of enrolment • Health plan
Mansouri, 2013[192]	Scotland	394,117	Combined	50–74	FOBT	Project record	The Scottish index of multiple deprivation (2009)	5th Quintile (least deprived)/ 1st Quintile (most deprived)	2.34	(2.27, 2.38)	• Age • Sex

Appendix B: Chapter 4 Socioeconomic Status and Risk of Colorectal Cancer: A Systematic Review and Meta-analysis

Appendix B table 1 Characteristics of the studies which measure effect of educational attainment on colon cancer risk

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Specific cancer site	Education (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Spadea, 2009[226]	Italy	1985–1999	2,061	Number of cases	30–74	Male	Non-specific	Non-specific	Primary or less/ at least high school	0.93	(0.83, 1.04)	• Stratified by sex
Egeberg, 2008[236]	Denmark	1994–2003	4,969	Number of all participants	≥30	Male	Non-specific	Non-specific	Basic or high school/ higher education	0.93	(0.85, 1.01)	• Calendar period • Age • Disposable income
Mouw, 2008[219]	United States	1995–1996	2,791	Number of cases	50–71	Male	Non-specific	Non-specific	Less than high school/ post graduate	1.10	(0.94, 1.29)	• Age • Race • Smoking • Alcohol consumptions g/day • Energy (Kcal/day) • Body mass index • Physical activity • Married • Family history of cancer
Pisa, 2000[225]	Italy	1992–1996	2,752	Number of all participants	Non-specific	Male	Non-specific	Non-specific	0–4 years/ >16 years	0.26	(0.15, 0.43)	• Age • Centre • Occupational physical activity • Total intake of energy • Vegetables and carbohydrates
Tavani, 1999[227]	Italy	1985–1996	5,138	Number of all participants	Non-specific	Male	Non-specific	Non-specific	<7 years/ ≥16 years)	0.41	(0.31, 0.53)	• Study/centre • Age • Coffee intake • Smoking • Alcohol • Vegetable intake
Van Loon, 1995[231]	Netherland	1986–1989	155	Number of cases	Non-specific	Male	Non-specific	Non-specific	Primary school/ higher vocational or university	1.00	(0.54, 1.85)	• Age • Quetelet index • Cholecystectomy • Alcohol intake • Large bowel cancer in family • Physical activity at work
Vecchia, 1992[229]	Italy	1983–1990	2,854	Number of all participants	<75	Male	Non-specific	Non-specific	<7 years/ ≥12 years	0.53	(0.40, 0.71)	• Age • Tobacco use • Alcohol consumption

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Specific cancer site	Education (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Spadea, 2009[226]	Italy	1985–1999	1,778	Number of cases	30–74	Female	Non-specific	Non-specific	Primary or less/ at least high school	0.93	(0.80, 1.07)	• Stratified by sex
Egeberg, 2008[236]	Denmark	1994–2003	4,684	Number of all participants	≥30	Female	Non-specific	Non-specific	Basic or high school/ higher education	1.02	(0.93, 1.12)	• Calendar period • Age • Disposable income
Mouw, 2008[219]	United States	1995–1996	1,282	Number of cases	50–71	Female	Non-specific	Non-specific	Less than high school/ post graduate	1.37	(1.06, 1.77)	• Age • Race • Smoking • Alcohol consumptions g/day • Energy (Kcal/day) • Body mass index • Physical activity • Married • Family history of cancer • Menopausal hormone therapy use
Braaten, 2005[237]	Norway	1991–2001	205	Number of cases	30–69	Female	Non-specific	Non-specific	7–9 years/ ≥17 years	1.23	(0.70, 2.17)	• Age
Pisa, 2000[225]	Italy	1992–1996	2,592	Number of all participants	Non-specific	Female	Non-specific	Non-specific	0–4 years/ >16 years	0.33	(0.18, 0.63)	• Age • Centre • Occupational physical activity • Total intake of energy • Vegetables and carbohydrates
Tavani, 1999[227]	Italy	1985–1996	4,104	Number of all participants	Non-specific	Female	Non-specific	Non-specific	<7 years/ ≥16 years	0.78	(0.53, 1.14)	• Study/centre • Age • Coffee intake • Smoking • Alcohol • Vegetable intake
Van Loon, 1995[231]	Netherland	1986–1989	153	Number of cases	Non-specific	Female	Non-specific	Non-specific	Primary school/ higher vocational or university	1.14	(0.50, 2.56)	• Age • Quetelet index • Cholecystectomy • Alcohol intake • Large bowel cancer in family • Physical activity at work

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Specific cancer site	Education (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Vecchia, 1992[229]	Italy	1983–1990	3,966	Number of all participants	<75	Female	Non-specific	Non-specific	<7 years/ ≥12 years	1.11	(0.77, 1.67)	• Age • Tobacco use • Alcohol consumption
Leufkens, 2012[240]	European countries	1991–2006	1,279	Number of cases	Non-specific	Combined	Non-specific	Non-specific	Primary education or less/ college or university	0.90	(0.76, 1.07)	• Body mass index • Physical activity • Alcohol • Intake of vegetables • Fruit • Fiber • Energy from fat • Energy from nonfat • Red meat • Processed meat • Fish • Smoking status • Smoking duration
Doubeni, 2012[141]	United States	1995–2006	2,050	Number of cases	50–73	Combined	Non-specific	Left colon cancer	<12 years/ post-graduate	1.29	(1.06, 1.56)	• Age • Sex • Race and ethnicity • Family history of colorectal cancer • State of residence • Behavioural factors • Neighbourhood socioeconomic status
Doubeni, 2012[141]	United States	1995–2006	3,537	Number of cases	50–72	Combined	Non-specific	Right colon cancer	<12 years/ post-graduate	1.07	(0.93, 1.24)	• Age • Sex • Race and ethnicity • Family history of colorectal cancer • State of residence • Behavioural factors • Neighbourhood socioeconomic status
Goy, 2008[223]	Canada	1992–1994	2,141	Number of all participants	25-65	Combined	Non-specific	Non-specific	Less than high school/ university	2.74	(1.95, 3.84)	• Age • Sex • All health risk factors

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity[#]	Specific cancer site	Education (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Pisa, 2000*[225]	Italy	1992–1996	5,344	Number of all participants	Non-specific	Combined	Non-specific	Non-specific	0-4 years/ >16 years	0.30	(0.21, 0.43)	• Age • Centre • Occupational physical activity • Total intake of energy • Vegetables and carbohydrates • Sex
Tavani, 1999*[227]	Italy	1985–1996	9,242	Number of all participants	Non-specific	Combined	Non-specific	Non-specific	<7 years/ ≥16 years	0.52	(0.42, 0.65)	• Study/centre • Age • Coffee intake • Smoking • Alcohol • Vegetable intake • Sex
Vecchia, 1992*[229]	Italy	1983–1990	6,820	Number of all participants	<75	Combined	Non-specific	Non-specific	<7 years/ ≥12 years	0.71	(0.59, 0.91)	• Age • Sex • Tobacco use • Alcohol consumption
Baquet, 1991[212]	United States	1978–1982	N/A	N/A	≥25	Combined	Caucasians	Non-specific	<12 years/ college graduate	0.92	(0.78, 1.07)	• Age
Baquet, 1991[212]	United States	1978–1982	N/A	N/A	≥25	Combined	African Americans	Non-specific	<12 years/ college graduate	0.77	(0.67, 0.89)	• Age

[#]Race/ethnicity categories as reported in the publication

*were not included in the meta-analyses

Acronyms: N/A=not available

Appendix B table 2 Characteristics of the studies which measure effect of educational attainment on rectal cancer risk

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Education (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Spadea, 2009[226]	Italy	1985–1999	1,106	Number of cases	30–74	Male	Non-specific	Primary or less/ at least high school	1.27	(1.07, 1.50)	• Stratified by sex
Egeberg, 2008[236]	Denmark	1994–2003	4,276	Number of all participants	≥30	Male	Non-specific	Basic or high school/ higher education	1.02	(0.93, 1.12)	• Calendar period • Age • Disposable income
Mouw, 2008[219]	United States	1995–1996	1,135	Number of cases	50–71	Male	Non-specific	Less than high school/ post graduate	1.50	(1.17, 1.92)	• Age • Race • Smoking • Alcohol consumptions g/day • Energy (Kcal/day) • Body mass index • Physical activity • Married • Family history of cancer
Pisa, 2000[225]	Italy	1992–1996	2,501	Number of all participants	Non-specific	Male	Non-specific	0–4 years/ >16 years	0.77	(0.42, 1.43)	• Age • Centre • Occupational physical activity • Total intake of energy • Vegetables and carbohydrates
Tavani, 1999[227]	Italy	1985–1996	4,763	Number of all participants	Non-specific	Male	Non-specific	<7 years/ ≥16 years	0.85	(0.59, 1.20)	• Study/centre • Age • Coffee intake • Smoking • Alcohol • Vegetable intake
Vecchia, 1992[229]	Italy	1983–1990	2,757	Number of all participants	<75	Male	Non-specific	<7 years/ ≥12 years	1.25	(0.83, 2.00)	• Age • Tobacco use • Alcohol consumption
Spadea, 2009[226]	Italy	1985–1999	860	Number of cases	30–74	Female	Non-specific	Primary or less/ at least high school	1.16	(0.94, 1.43)	• Stratified by sex
Egeberg, 2008[236]	Denmark	1994–2003	2,901	Number of all participants	≥30	Female	Non-specific	Basic or high school/ higher education	1.12	(1.00, 1.27)	• Calendar period • Age • Disposable income

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Education (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Mouw, 2008[219]	United States	1995–1996	461	Number of cases	50–71	Female	Non-specific	Less than high school/ post graduate	1.05	(0.68, 1.62)	• Age • Race • Smoking • Alcohol consumptions g/day • Energy (Kcal/day) • Body mass index • Physical activity • Married • Family history of cancer • Menopausal hormone therapy use
Braaten, 2005[237]	Norway	1991–2001	112	Number of cases	30–69	Female	Non-specific	7–9 years/ ≥17 years	0.63	(0.33, 1.20)	• Age
Pisa, 2000[225]	Italy	1992–1996	2,349	Number of all participants	Non-specific	Female	Non-specific	0–4 years/ >16 years	0.31	(0.14, 0.67)	• Age • Centre • Occupational physical activity • Total intake of energy • Vegetables and carbohydrates
Tavani, 1999[227]	Italy	1985–1996	3,652	Number of all participants	Non-specific	Female	Non-specific	<7 years/ ≥16 years	0.99	(0.60, 1.64)	• Study/centre • Age • Coffee intake • Smoking • Alcohol • Vegetable intake
Vecchia, 1992[229]	Italy	1983–1990	3,796	Number of all participants	<75	Female	Non-specific	<7 years/ ≥12 years	1.11	(0.71, 2.00)	• Age • Tobacco use • Alcohol consumption
Leufkens, 2012[240]	European countries	1991–2006	727	Number of cases	Non-specific	Combined	Non-specific	Primary education or less/ college or university	0.92	(0.74, 1.15)	• Body mass index • Physical activity • Alcohol • Intake of vegetables • Fruit • Fiber • Energy from fat • Energy from nonfat • Red meat • Processed meat • Fish • Smoking status • Smoking duration

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity[#]	Education (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Doubeni, 2012[141]	United States	1995–2006	1,991	Number of cases	50–74	Combined	Non-specific	<12 years/ post-graduate	1.36	(1.11, 1.65)	• Age • Sex • Race and ethnicity • Family history of colorectal cancer • State of residence • Behavioural factors • Neighbourhood socioeconomic status
Goy, 2008[223]	Canada	1992–1994	2,107	Number of all participants	25–65	Combined	Non-specific	Less than high school/ university	2.19	(1.53, 2.97)	• Age • Sex • All health risk factors
Pisa, 2000*[225]	Italy	1992–1996	4,850	Number of all participants	Non-specific	Combined	Non-specific	0–4 years/ >16 years	0.56	(0.34, 0.91)	• Age • Centre • Occupational physical activity • Total intake of energy • Vegetables and carbohydrates • Sex
Tavani, 1999*[227]	Italy	1985–1996	8,415	Number of all participants	Non-specific	Combined	Non-specific	<7 years/ ≥16 years	0.88	(0.66, 1.18)	• Study/centre • Age • Coffee intake • Smoking • Alcohol • Vegetable intake • Sex
Vecchia, 1992*[229]	Italy	1983–1990	6,553	Number of all participants	<75	Combined	Non-specific	<7 years/ ≥12 years	1.11	(0.83, 1.67)	• Age • Sex • Tobacco use • Alcohol consumption
Baquet, 1991[212]	United States	1978–1982	N/A	N/A	≥25	Combined	Caucasians	<12 years/ college graduate	1.05	(0.82, 1.35)	• Age
Baquet, 1991[212]	United States	1978–1982	N/A	N/A	≥25	Combined	African Americans	<12 years/ college graduate	2.67	(1.80, 4.03)	• Age

[#]Race/ethnicity categories as reported in the publication

*were not included in the meta-analyses

Acronyms: N/A=not available

Appendix B table 3 Characteristics of the studies which measure effect of educational attainment on colorectal cancer risk

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity[#]	Education (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Faggiano, 1994[228]	Italy	1981–1989	427	Number of cases	Non-specific	Male	Non-specific	Primary school/ university	0.48	(0.33, 0.71)	• Age • Birth area • Housing tenure • SES group
Faggiano, 1994[228]	Italy	1981–1989	353	Number of cases	Non-specific	Female	Non-specific	Primary school/ university	0.71	(0.38, 1.32)	• Age • Birth area • Housing tenure • SES group
Leufkens, 2012*[240]	European countries	1991–2006	2,006	Number of cases	Non-specific	Combined	Non-specific	Primary education or less/ college or university	0.91	(0.79, 1.04)	• Body mass index • Physical activity • Alcohol • Intake of vegetables • Fruit • Fiber • Energy from fat • Energy from nonfat • Red meat • Processed meat • Fish • Smoking status • Smoking duration
Doubeni, 2012*[141]	United States	1995–2006	7,676	Number of cases	50–71	Combined	Non-specific	<12 years/ post-graduate	1.19	(1.07, 1.31)	• Age • Sex • Race and ethnicity • Family history of colorectal cancer • State of residence • Behavioural factors • Neighbourhood socioeconomic status
Clegg, 2009[214]	United States	1973–2001	1,467	Number of cases	≥25	Combined	Non-specific	Less than high school/ college education or beyond	1.45	(1.31, 1.61)	• Age • Sex • CPS cohort
de Kok, 2008[230]	Netherland	1991–2005	12,981	Number of all participants	15–74	Combined	Non-specific	Primary school/ higher vocational school and university	0.98	(0.60, 1.60)	• Age • Sex • Marital status

[#]Race/ethnicity categories as reported in the publication

*were not included in the meta-analyses

Appendix B table 4 Characteristics of the studies which measure effect of income on colon cancer risk

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Income (comparison/ reference)	OR	(95%CI)	Adjusted confounders
Kim, 2012[241]	Korea	2009	2,503	Number of cases	Non-specific	Male	Koreans	Income class: class 5 (lowest SES)/ class 1 (highest SES)	0.92	(0.81, 1.05)	• Age • Residence
Mackillop, 2000[218]	Canada	1990–1991	N/A	N/A	Non-specific	Male	Non-specific	Median household income: 1st decile (lowest SES)/ 10th decile (highest SES)	1.20	(1.10, 1.33)	• Age
Mackillop, 2000[218]	United States	1990–1991	N/A	N/A	Non-specific	Male	Non-specific	Median household income: 1st decile (lowest SES)/ 10th decile (highest SES)	1.08	(1.01, 1.14)	• Age
Gorey, 1998[222]	Canada	1986–1993	1,372	Number of cases	≥25	Male	Non-specific	Income: lowest income quintile/ highest income quintile	1.11	(1.02, 1.20)	• Age
Gorey, 1995[215]	United States	1979–1986	3,639	Number of cases	Non-specific	Male	Caucasians	Census tract poverty status: lowest SES/ highest SES	1.39	(1.24, 1.55)	• Age
Gorey, 1995[215]	United States	1979–1986	186	Number of cases	Non-specific	Male	African Americans	Census tract poverty status: lowest SES/ highest SES	1.71	(1.31, 2.24)	• Age
Kim, 2012[241]	Korea	2009	1,776	Number of cases	Non-specific	Female	Koreans	Income Class: class 5 (lowest SES)/ class 1 (highest SES)	1.12	(0.97,1.30)	• Age • Residence
Mackillop, 2000[218]	Canada	1990–1991	N/A	N/A	Non-specific	Female	Non-specific	Median household income: 1st decile (lowest SES)/ 10th decile (highest SES)	1.15	(1.05, 1.28)	• Age
Mackillop, 2000[218]	United States	1990–1991	N/A	N/A	Non-specific	Female	Non-specific	Median household income: 1st decile (lowest SES)/ 10th decile (highest SES)	1.10	(1.03, 1.16)	• Age
Gorey, 1998[222]	Canada	1986–1993	1,294	Number of cases	≥25	Female	Non-specific	Income: lowest income quintile/ highest income quintile	0.99	(0.97, 1.01)	• Age
Gorey 1995[215]	United States	1979–1986	4,049	Number of cases	Non-specific	Female	Caucasians	Census tract poverty status: lowest SES/ highest SES	1.48	(1.33, 1.65)	• Age

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Income (comparison/ reference)	OR	(95%CI)	Adjusted confounders
Gorey, 1995[215]	United States	1979–1986	213	Number of cases	Non-specific	Female	African Americans	Census tract poverty status: lowest SES/ highest SES	1.62	(1.28, 2.05)	• Age
Baquet, 1991[212]	United States	1978–1982	N/A	N/A	≥25	Combined	Caucasians	Median annual family income: <$15,000/ >$30,000	1.00	(0.87, 1.16)	• Age
Baquet, 1991[212]	United States	1978–1982	N/A	N/A	≥25	Combined	African Americans	Median annual family income: <$15,000/ >$30,000	0.75	(0.65, 0.87)	• Age

#Race/ethnicity categories as reported in the publication

Acronyms: N/A=not available

Appendix B table 5 Characteristics of the studies which measure effect of income on rectal cancer risk

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Income (comparison/ reference)	OR	(95%CI)	Adjusted confounders
Kim, 2012[241]	Korea	2009	2,049	Number of cases	Non-specific	Male	Koreans	Income Class: class 5 (lowest SES)/ class 1 (highest SES)	1.37	(1.18, 1.59)	• Age • Residence
Mackillop, 2000[218]	Canada	1990–1991	N/A	N/A	Non-specific	Male	Non-specific	Median household income: 1st decile (lowest SES)/ 10th decile (highest SES)	1.23	(1.09, 1.43)	• Age
Mackillop, 2000[218]	United States	1990–1991	N/A	N/A	Non-specific	Male	Non-specific	Median household income: 1st decile (lowest SES)/ 10th decile (highest SES)	1.19	(1.10, 1.32)	• Age
Gorey, 1998[222]	Canada	1986–1993	689	Number of cases	≥25	Male	Non-specific	Income: lowest income quintile/ highest income quintile	1.25	(1.08, 1.44)	• Age
Gorey, 1995[215]	United States	1979–1986	1,853	Number of cases	Non-specific	Male	Caucasians	Census tract poverty status: lowest SES/ highest SES	1.36	(1.16, 1.60)	• Age
Gorey, 1995[215]	United States	1979–1986	77	Number of cases	Non-specific	Male	African Americans	Census tract poverty status: lowest SES/ highest SES	1.59	(1.04, 2.44)	• Age
Kim, 2012[241]	Korea	2009	1,227	Number of cases	Non-specific	Female	Koreans	Income Class: class 5 (lowest SES)/ class 1 (highest SES)	1.29	(1.08, 1.53)	• Age • Residence
Mackillop, 2000[218]	Canada	1990–1991	N/A	N/A	Non-specific	Female	Non-specific	Median household income: 1st decile (lowest SES)/ 10th decile (highest SES)	1.06	(0.91, 1.27)	• Age
Mackillop, 2000[218]	United States	1990–1991	N/A	N/A	Non-specific	Female	Non-specific	Median household income: 1st decile (lowest SES)/ 10th decile (highest SES)	1.10	(1.00, 1.22)	• Age

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Income (comparison/ reference)	OR	(95%CI)	Adjusted confounders
Gorey, 1998[222]	Canada	1986–1993	460	Number of cases	≥25	Female	Non-specific	Income: lowest income quintile/ highest income quintile	1.04	(1.01, 1.07)	• Age
Gorey, 1995[215]	United States	1979–1986	1,457	Number of cases	Non-specific	Female	Caucasians	Census tract poverty status: lowest SES/ highest SES	1.64	(1.39, 1.94)	• Age
Gorey, 1995[215]	United States	1979–1986	60	Number of cases	Non-specific	Female	African Americans	Census tract poverty status: lowest SES/ highest SES	1.92	(1.21, 3.05)	• Age
Baquet, 1991[212]	United States	1978–1982	N/A	N/A	≥25	Combined	Caucasians	Median annual family income: <$15,000/ >$30,000	1.41	(1.11, 1.79)	• Age
Baquet, 1991[212]	United States	1978–1982	N/A	N/A	≥25	Combined	African Americans	Median annual family income: <$15,000/ >$30,000	0.95	(0.74, 1.23)	• Age

#Race/ethnicity categories as reported in the publication

Acronyms: N/A=not available

Appendix B table 6 Characteristics of the studies which measure effect of income on colorectal cancer risk

Author, year	Country of participants recruitment	Reference year	N	Target age group	Sex-specific analyses	Race/ ethnicity[#]	Income (comparison/ reference)	OR	(95%CI)	Adjusted confounders
Liu, 2016[217]	United States	2008–2011	N/A	Non-specific	Combined	Non-Hispanic Caucasians	Median household income: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.14	(1.05, 1.22)	• Age • Gender
Liu, 2016[217]	United States	2008–2011	N/A	Non-specific	Combined	Non-Hispanic African Americans	Median household income: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.92	(1.49, 2.50)	• Age • Gender
Liu, 2016[217]	United States	2008–2011	N/A	Non-specific	Combined	Hispanics	Median household income: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.05	(0.98, 1.12)	• Age • Gender
Liu, 2016[217]	United States	2008–2011	N/A	Non-specific	Combined	Asian/ Pacific Islander/ American Indians/ unspecific	Median household income: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.89	(0.85, 4.17)	• Age • Gender
Liu, 2016[217]	United States	2004–2007	N/A	Non-specific	Combined	Non-Hispanic Caucasians	Median household income: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.16	(1.09, 1.27)	• Age • Gender
Liu, 2016[217]	United States	2004–2007	N/A	Non-specific	Combined	Non-Hispanic African Americans	Median household income: 1st Quintile (low SES)/ 5th Quintile (high SES)	2.04	(1.61, 2.56)	• Age • Gender
Liu, 2016[217]	United States	2004–2007	N/A	Non-specific	Combined	Hispanics	Median household income: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.01	(0.94, 1.08)	• Age • Gender
Liu, 2016[217]	United States	2004–2007	N/A	Non-specific	Combined	Asian/ Pacific Islander/ American Indians/ unspecific	Median household income: 1st Quintile (low SES)/ 5th Quintile (high SES)	7.69	(3.70, 16.67)	• Age • Gender
Liu, 2016[217]	United States	2000–2003	N/A	Non-specific	Combined	Non-Hispanic Caucasians	Median household income: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.09	(1.02, 1.18)	• Age • Gender
Liu, 2016[217]	United States	2000–2003	N/A	Non-specific	Combined	Non-Hispanic African Americans	Median household income: 1st Quintile (low SES)/ 5th Quintile (high SES)	2.17	(1.69, 2.78)	• Age • Gender
Liu, 2016[217]	United States	2000–2003	N/A	Non-specific	Combined	Hispanics	Median household income: 1st Quintile (low SES)/ 5th Quintile (high SES)	0.96	(0.90, 1.03)	• Age • Gender
Liu, 2016[217]	United States	2000–2003	N/A	Non-specific	Combined	Asian/ Pacific Islander/ American Indians/ unspecific	Median household income: 1st Quintile (low SES)/ 5th Quintile (high SES)	7.14	(2.86, 16.67)	• Age • Gender

Author, year	Country of participants recruitment	Reference year	N	Target age group	Sex-specific analyses	Race/ ethnicity#	Income (comparison/ reference)	OR	(95%CI)	Adjusted confounders
Liu, 2016[217]	United States	1995–1999	N/A	Non-specific	Combined	Non-Hispanic Caucasians	Median household income: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.01	(0.94, 1.08)	• Age • Gender
Liu, 2016[217]	United States	1995–1999	N/A	Non-specific	Combined	Non-Hispanic African Americans	Median household income: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.56	(1.25, 1.96)	• Age • Gender
Liu 2016[217]	United States	1995–1999	N/A	Non-specific	Combined	Hispanics	Median household income: 1st Quintile (low SES)/ 5th Quintile (high SES)	0.88	(0.81, 0.94)	• Age • Gender
Liu, 2016[217]	United States	1995–1999	N/A	Non-specific	Combined	Asian/ Pacific Islander/ American Indians/ unspecific	Median household income: 1st Quintile (low SES)/ 5th Quintile (high SES)	8.33	(3.57, 16.67)	• Age • Gender
Clegg, 2009[214]	United States	1973–2001	1,467	≥25	Combined	Non-specific	Family income: <$12,500/ $>50,000	1.20	(1.02, 1.43)	• Age • Sex • The Census Bureau's Current Population Survey cohort

#Race/ethnicity categories as reported in the publication

Acronyms: N/A=not available

Appendix B table 7 Characteristics of the studies which measure effect of composite indicators based on area of residence on colon cancer risk

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Specific cancer site	Composite indicators (comparison/ reference)	OR	(95%CI)	Adjusted confounders
Miki, 2014[242]	Japan	1990–2009	40,883	Number of all participants	40–69	Male	Japanese	Non-specific	The Japanese deprivation index: 4th quartile (most deprived)/ 1st quartile (least deprived)	0.87	(0.62, 1.24)	• Age • Area, population density (quartile) • Occupation • Smoking • Alcohol drinking • Body mass index • Leisure-time sport activity.
Smith, 1996[243]	Australia	1987–1991	3,549	Number of cases	Non-specific	Male	Non-specific	Non-specific	Index of relative socioeconomic disadvantage: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.12	(1.02, 1.25)	• Age
Miki, 2014[242]	Japan	1990–2009	45,229	Number of all participants	40–69	Female	Japanese	Non-specific	The Japanese deprivation index: 4th quartile (most deprived)/ 1st quartile (least deprived)	1.03	(0.72, 1.47)	• Age • Area, population density (quartile) • Occupation • Smoking • Alcohol drinking • Body mass index • Leisure-time sport activity.
Kim, 2010[80]	United States	1986–2006	1,223	Number of cases	30–55	Female	Non-specific	Non-specific	Neighbourhood socioeconomic score: 1st Quintile (lowest SES)/ 5th Quintile (highest SES)	1.10	(0.91, 1.35)	• Neighbourhood percentage black • Immigrant concentration, and residential stability • Age • Race/ethnicity • Educational attainment • Husband's educational attainment • Family history of colorectal cancer • History of polyp
Smith, 1996[243]	Australia	1987–1991	3,444	Number of cases	Non-specific	Female	Non-specific	Non-specific	Index of relative socioeconomic disadvantage: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.18	(1.06, 1.32)	• Age

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Specific cancer site	Composite indicators (comparison/ reference)	OR	(95%CI)	Adjusted confounders
Steinbrecher, 2012*[220]	United States	1998–2002	14,969	Number of cases	Non-specific	Combined	Non-specific	Left colon cancer	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.08	(1.02, 1.14)	• Age
Steinbrecher, 2012[220]	United States	1998–2002	10,204	Number of cases	Non-specific	Combined	Non-Hispanic Caucasians	Left colon cancer	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.30	(1.20, 1.39)	• Age
Steinbrecher, 2012[220]	United States	1998–2002	1,039	Number of cases	Non-specific	Combined	African Americans	Left colon cancer	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.39	(1.03, 1.92)	• Age
Steinbrecher, 2012[220]	United States	1998–2002	1,856	Number of cases	Non-specific	Combined	Hispanics	Left colon cancer	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	0.67	(0.56, 0.80)	• Age
Steinbrecher, 2012[220]	United States	1998–2002	1,870	Number of cases	Non-specific	Combined	Asian/ Pacific Islander	Left colon cancer	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.02	(0.87, 1.20)	• Age
Steinbrecher, 2012*[220]	United States	1998–2002	20,560	Number of cases	Non-specific	Combined	Non-specific	Right colon cancer	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	0.92	(0.88, 0.96)	• Age
Steinbrecher, 2012[220]	United States	1998–2002	15,247	Number of cases	Non-specific	Combined	Non-Hispanic Caucasians	Right colon cancer	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.10	(1.03, 1.18)	• Age
Steinbrecher, 2012[220]	United States	1998–2002	1,505	Number of cases	Non-specific	Combined	African Americans	Right colon cancer	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.06	(0.85, 1.37)	• Age
Steinbrecher, 2012[220]	United States	1998–2002	2,257	Number of cases	Non-specific	Combined	Hispanics	Right colon cancer	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	0.54	(0.46, 0.63)	• Age
Steinbrecher, 2012[220]	United States	1998–2002	1,551	Number of cases	Non-specific	Combined	Asian/ Pacific Islander	Right colon cancer	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	0.83	(0.69, 0.99)	• Age

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity[#]	Specific cancer site	Composite indicators (comparison/ reference)	OR	(95%CI)	Adjusted confounders
Doubeni, 2012[141]	United States	1995–2006	2,050	Number of cases	50–77	Combined	Non-specific	Left colon cancer	Neighbour deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.18	(0.98, 1.43)	• Age • Sex • Race and ethnicity • Family history of colorectal cancer • State of residence • Behavioural factors • Education.
Doubeni, 2012[141]	United States	1995–2006	3,537	Number of cases	50–76	Combined	Non-specific	Right colon cancer	Neighbour deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.08	(0.94, 1.25)	• Age • Sex • Race and ethnicity • Family history of colorectal cancer • State of residence • Behavioural factors • Education.

[#]Race/ethnicity categories as reported in the publication

*were not included in the meta-analyses

Appendix B table 8 Characteristics of the studies which measure effect of composite indicators based on area of residence on rectal cancer risk

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Composite indicators (comparison/ reference)	OR	(95%CI)	Adjusted confoundiers
Miki, 2014[242]	Japan	1990–2009	40,883	Number of all participants	40–69	Male	Japanese	The Japanese deprivation index: 4th quartile (most deprived)/ 1st quartile (least deprived)	0.54	(0.36, 0.82)	• Age • Area, population density (quartile) • Occupation • Smoking • Alcohol drinking • Body mass index • Leisure-time sport activity.
Smith, 1996[243]	Australia	1987–1991	2,193	Number of cases	Non-specific	Male	Non-specific	Index of relative socioeconomic disadvantage: 1st Quintile (low SES)/ 5th Quintile (high SES)	0.85	(0.75, 0.97)	• Age
Miki, 2014[242]	Japan	1990–2009	45,229	Number of all participants	40–69	Female	Japanese	The Japanese deprivation index: 4th quartile (most deprived)/ 1st quartile (least deprived)	0.54	(0.32, 0.92)	• Age • Area, population density (quartile) • Occupation • Smoking • Alcohol drinking • Body mass index • Leisure-time sport activity.
Kim, 2010[80]	United States	1986–2006	305	Number of cases	30–55	Female	Non-specific	Neighbourhood socioeconomic score: 1st Quintile (lowest SES)/ 5th Quintile (highest SES)	1.56	(1.08, 2.27)	• Neighbourhood percentage black • Immigrant concentration, and residential stability • Age • Race/ethnicity • Educational attainment • Husband's educational attainment • Family history of colorectal cancer • History of polyp
Smith, 1996[243]	Australia	1987–1991	1,483	Number of cases	Non-specific	Female	Non-specific	Index of relative socioeconomic disadvantage: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.16	(0.97, 1.33)	• Age
Steinbrecher, 2012*[220]	United States	1998–2002	14,828	Number of cases	Non-specific	Combined	Non-specific	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.14	(1.08, 1.20)	• Age

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Composite indicators (comparison/ reference)	OR	(95%CI)	Adjusted confounding factors
Steinbrecher, 2012[220]	United States	1998–2002	10,293	Number of cases	Non-specific	Combined	Non-Hispanic Caucasians	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.41	(1.32, 1.54)	• Age
Steinbrecher, 2012[220]	United States	1998–2002	756	Number of cases	Non-specific	Combined	African Americans	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.27	(0.88, 1.82)	• Age
Steinbrecher, 2012[220]	United States	1998–2002	2,050	Number of cases	Non-specific	Combined	Hispanics	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	0.75	(0.63, 0.89)	• Age
Steinbrecher, 2012[220]	United States	1998–2002	1,729	Number of cases	Non-specific	Combined	Asian/ Pacific Islander	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.04	(0.88, 1.23)	• Age
Doubeni, 2012[141]	United States	1995–2006	1,991	Number of cases	50–76	Combined	Non-specific	Neighbour deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.31	(1.08, 1.59)	• Age • Sex • Race and ethnicity • Family history of colorectal cancer • State of residence • Behavioural factors • Education.

#Race/ethnicity categories as reported in the publication

*were not included in the meta-analyses

Appendix B table 9 Characteristics of the studies which measure effect of composite indicators based on area of residence on colorectal cancer risk

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Composite indicators (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Tweed, 2018[235]	Scotland	2010–2012	82.4	Crude incidence (per 100,000 person-years)	Non-specific	Male	Non-specific	Scottish index of multiple deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.24	(1.11, 1.39)	• Age
Tweed, 2018[235]	Scotland	2007–2009	80.9	Crude incidence (per 100,000 person-years)	Non-specific	Male	Non-specific	Scottish index of multiple deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.15	(1.03, 1.29)	• Age
Tweed, 2018[235]	Scotland	2004–2006	73.3	Crude incidence (per 100,000 person-years)	Non-specific	Male	Non-specific	Scottish index of multiple deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.13	(1.01, 1.28)	• Age
Tweed, 2018[235]	Scotland	2001–2003	72.6	Crude incidence (per 100,000 person-years)	Non-specific	Male	Non-specific	Scottish index of multiple deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.03	(0.91, 1.16)	• Age
Canchola, 2017*[213]	United States	1993–2010	35,397	Number of all participants	Non-specific	Male	Non-specific	Neighbourhood socioeconomic status: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.06	(0.77, 1.45)	• Clustering effect of block group • Age • Race/ethnicity • Body mass index • Family history of colorectal cancer • History of intestinal polyps • Education • Pack-years of smoking • Multivitamin use • Nonsteroidal anti-inflammatory medication use • Alcohol consumption • Vigorous physical activity • History of diabetes • Calories • Red meat • Dietary fiber • Calcium • Folacin • Vitamin D • All the neighbourhood variables

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Composite indicators (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Canchola, 2017[213]	United States	1993–2010	9,190	Number of all participants	Non-specific	Male	African Americans	Neighbourhood socioeconomic status: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.07	(0.56, 2.02)	• Clustering effect of block group • Age • Body mass index • Family history of colorectal cancer • History of intestinal polyps • Education • Pack-years of smoking • Multivitamin use • Nonsteroidal anti-inflammatory medication use • Alcohol consumption • Vigorous physical activity • History of diabetes • Calories • Red meat • Dietary fiber • Calcium • Folacin • Vitamin D • All the neighbourhood variables
Canchola, 2017[213])	United States	1993–2010	5,222	Number of all participants	Non-specific	Male	Japanese Americans	Neighbourhood socioeconomic status: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.36	(0.57, 3.26)	• Clustering effect of block group • Age • Body mass index • Family history of colorectal cancer • History of intestinal polyps • Education • Pack-years of smoking • Multivitamin use • Nonsteroidal anti-inflammatory medication use • Alcohol consumption • Vigorous physical activity • History of diabetes • Calories • Red meat • Dietary fiber • Calcium • Folacin • Vitamin D • All the neighbourhood variables

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Composite indicators (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Canchola, 2017[213]	United States	1993–2010	16,724	Number of all participants	Non-specific	Male	Latinos	Neighbourhood socioeconomic status: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.07	(0.64, 1.78)	• Clustering effect of block group • Age • Body mass index • Family history of colorectal cancer • History of intestinal polyps • Education • Pack-years of smoking • Multivitamin use • Nonsteroidal anti-inflammatory medication use • Alcohol consumption • Vigorous physical activity • History of diabetes • Calories • Red meat • Dietary fiber • Calcium • Folacin • Vitamin D • All the neighbourhood variables
Canchola, 2017[213]	United States	1993–2010	4,261	Number of all participants	Non-specific	Male	Caucasians	Neighbourhood socioeconomic status: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.33	(0.48, 3.72)	• Clustering effect of block group • Age • Body mass index • Family history of colorectal cancer • History of intestinal polyps • Education • Pack-years of smoking • Multivitamin use • Nonsteroidal anti-inflammatory medication use • Alcohol consumption • Vigorous physical activity • History of diabetes • Calories • Red meat • Dietary fiber • Calcium • Folacin • Vitamin D • All the neighbourhood variables
Hastert, 2015[216]	United States	2000–2010	26,926	Number of all participants	50–76	Male	Non-specific	Quintiles of area-level SES index: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.53	(0.99, 2.38)	• Age • Race/ethnicity • Marital status • Education • Annual household income
Garcia-Gil, 2014[239]	Spain	2009–2012	N/A	N/A	Non-specific	Male	Non-specific	The ecological MEDEA index: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	0.89	(0.82, 0.97)	• Age • Obesity • Hypertension • Diabetes • SIDIAP codes for current smoking • High-risk alcohol intake

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Composite indicators (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Miki, 2014*[242]	Japan	1990–2009	40,883	Number of all participants	40–69	Male	Japanese	The Japanese deprivation index quartile: 4th Quartile (most deprived)/ 1st Quartile (least deprived)	0.75	(0.57, 0.98)	• Age • Area, population density (quartile) • Occupation • Smoking • Alcohol drinking • Body mass index • Leisure-time sport activity.
Kuznetsov, 2012[238]	Germany	2003–2006	16,151	Number of cases	Non-specific	Male	Non-specific	Bavarian index of multiple deprivation quintile: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.30	(1.22, 1.38)	• Age
Torres-Cintron, 2012[224]	Puerto Rico	2000–2004	N/A	N/A	Non-specific	Male	Non-specific	Socioeconomic position index: SEP1 (lowest SES)/ SEP5 (highest SES)	0.76	(0.66, 0.87)	• Age
Torres-Cintron, 2012[224]	Puerto Rico	1995–1999	N/A	N/A	Non-specific	Male	Non-specific	Socioeconomic position index: SEP1 (lowest SES)/ SEP5 (highest SES)	0.74	(0.64, 0.85)	• Age
Oliphant, 2011[234]	Scotland	2005–2007	2,568	Number of cases	Non-specific	Male	Non-specific	Scottish index of multiple deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.21	(1.08, 1.35)	• Age
Oliphant, 2011[234]	Scotland	2002–2004	2,544	Number of cases	Non-specific	Male	Non-specific	Scottish index of multiple deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.10	(0.99, 1.23)	• Age
Oliphant, 2011[234]	Scotland	1999–2001	2,424	Number of cases	Non-specific	Male	Non-specific	Scottish index of multiple deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.00	(0.90, 1.12)	• Age

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Composite indicators (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Tweed, 2018[235]	Scotland	2010–2012	63.4	Crude incidence (per 100,000 person-years)	Non-specific	Female	Non-specific	Scottish index of multiple deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.20	(1.06, 1.36)	• Age
Tweed, 2018[235]	Scotland	2007–2009	61.9	Crude incidence (per 100,000 person-years)	Non-specific	Female	Non-specific	Scottish index of multiple deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.10	(0.97, 1.24)	• Age
Tweed, 2018[235]	Scotland	2004–2006	58.9	Crude incidence (per 100,000 person-years)	Non-specific	Female	Non-specific	Scottish index of multiple deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.03	(0.90, 1.17)	• Age
Tweed, 2018[235]	Scotland	2001–2003	57.1	Crude incidence (per 100,000 person-years)	Non-specific	Female	Non-specific	Scottish index of multiple deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	0.93	(0.82, 1.06)	• Age
Canchola, 2017*[213]	United States	1993–2010	45,800	Number of all participants	Non-specific	Female	Non-specific	Neighbourhood socioeconomic status: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.06	(0.78, 1.43)	• Clustering effect of block group • Age • Race/ethnicity • Body mass index • Family history of colorectal cancer • History of intestinal polyps • Education • Pack-years of smoking • Multivitamin use • Nonsteroidal anti-inflammatory medication use • Alcohol consumption • Vigorous physical activity • History of diabetes • Calories • Red meat • Dietary fiber • Calcium • Folacin • Vitamin D • All the neighbourhood variables

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Composite indicators (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Canchola, 2017[213]	United States	1993–2010	15,903	Number of all participants	Non-specific	Female	African Americans	Neighbourhood socioeconomic status: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.14	(0.70, 1.84)	• Clustering effect of block group • Age • Body mass index • Family history of colorectal cancer • History of intestinal polyps • Education • Pack-years of smoking • Multivitamin use • Nonsteroidal anti-inflammatory medication use • Alcohol consumption • Vigorous physical activity • History of diabetes • Calories • Red meat • Dietary fiber • Calcium • Folacin • Vitamin D • All the neighbourhood variables
Canchola, 2017[213]	United States	1993–2010	5,415	Number of all participants	Non-specific	Female	Japanese Americans	Neighbourhood socioeconomic status: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.07	(0.38, 2.98)	• Clustering effect of block group • Age • Body mass index • Family history of colorectal cancer • History of intestinal polyps • Education • Pack-years of smoking • Multivitamin use • Nonsteroidal anti-inflammatory medication use • Alcohol consumption • Vigorous physical activity • History of diabetes • Calories • Red meat • Dietary fiber • Calcium • Folacin • Vitamin D • All the neighbourhood variables

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Composite indicators (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Canchola, 2017[213]	United States	1993–2010	16,836	Number of all participants	Non-specific	Female	Latinos	Neighbourhood socioeconomic status: 1st Quintile (low SES)/ 5th Quintile (high SES)	0.83	(0.43, 1.57)	• Clustering effect of block group • Age • Body mass index • Family history of colorectal cancer • History of intestinal polyps • Education • Pack-years of smoking • Multivitamin use • Nonsteroidal anti-inflammatory medication use • Alcohol consumption • Vigorous physical activity • History of diabetes • Calories • Red meat • Dietary fiber • Calcium • Folacin • Vitamin D • All the neighbourhood variables
Canchola, 2017[213]	United States	1993–2010	7,646	Number of all participants	Non-specific	Female	Caucasians	Neighbourhood socioeconomic status: 1st Quintile (low SES)/ 5th Quintile (high SES)	0.90	(0.34, 2.40)	• Clustering effect of block group • Age • Body mass index • Family history of colorectal cancer • History of intestinal polyps • Education • Pack-years of smoking • Multivitamin use • Nonsteroidal anti-inflammatory medication use • Alcohol consumption • Vigorous physical activity • History of diabetes • Calories • Red meat • Dietary fiber • Calcium • Folacin • Vitamin D • All the neighbourhood variables
Hastert, 2015[216]	United States	2000–2010	25,260	Number of all participants	50–76	Female	Non-specific	Quintiles of area-level SES index: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.18	(0.72, 1.93)	• Age • Race/ethnicity • Marital status • Education • Annual household income

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity#	Composite indicators (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Garcia-Gil, 2014[239]	Spain	2009–2012	N/A	N/A	Non-specific	Female	Non-specific	The ecological MEDEA index: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	0.90	(0.82, 1.00)	• Age • Obesity • Hypertension • Diabetes • Smoking • High-risk alcohol intake
Miki, 2014*[242]	Japan	1990–2009	45,229	Number of all participants	40–69	Female	Japanese	The Japanese deprivation index quartile: 4th Quartile (most deprived)/ 1st Quartile (least deprived)	0.85	(0.63, 1.15)	• Age • Area, population density (quartile) • Occupation • Smoking • Alcohol drinking • Body mass index • Leisure-time sport activity.
Kuznetsov, 2012[238]	Germany	2003–2006	13,424	Number of cases	Non-specific	Female	Non-specific	Bavarian index of multiple deprivation quintile: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.19	(1.11, 1.27)	• Age
Torres-Cintron, 2012[224]	Puerto Rico	2000–2004	N/A	N/A	Non-specific	Female	Non-specific	Socioeconomic position index: SEP1 (lowest SES)/ SEP5 (highest SES)	0.81	(0.70, 0.94)	• Age
Torres-Cintron, 2012[224]	Puerto Rico	1995–1999	N/A	N/A	Non-specific	Female	Non-specific	Socioeconomic position index: SEP1 (lowest SES)/ SEP5 (highest SES)	0.83	(0.71, 0.98)	• Age
Oliphant, 2011[234]	Scotland	2005–2007	2,219	Number of cases	Non-specific	Female	Non-specific	Scottish index of multiple deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.04	(0.90, 1.20)	• Age
Oliphant, 2011[234]	Scotland	2002–2004	2,113	Number of cases	Non-specific	Female	Non-specific	Scottish index of multiple deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.01	(0.87, 1.17)	• Age

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity[#]	Composite indicators (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Oliphant, 2011[234]	Scotland	1999–2001	2,183	Number of cases	Non-specific	Female	Non-specific	Scottish index of multiple deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.02	(0.89, 1.18)	• Age
Stroup, 2017[221]	United States	1945–2009	105,618	Number of all participants	Non-specific	Combined	Non-specific	Neighbourhood SES: 1st Quartile (lowest SES)/ 4th Quartile (highest SES)	1.25	(0.88, 1.80)	• Birth weight • Year of birth • Sibling in cohort • Sex
Hastert, 2015*[216]	United States	2000–2010	52,186	Number of all participants	50–76	Combined	Non-specific	Quintiles of area-level SES index: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.35	(0.97, 1.88)	• Age • Race/ethnicity • Marital status • Education • Annual household income
Garcia-Gil, 2014*[239]	Spain	2009–2012	N/A	N/A	Non-specific	Combined	Non-specific	The ecological MEDEA index: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	0.90	(0.84, 0.95)	• Age • Sex • Obesity • Hypertension • Diabetes • Smoking • High-risk alcohol intake
Steinbrecher, 2012*[220]	United States	1998–2002	52,608	Number of cases	Non-specific	Combined	Non-specific	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.03	(1.00, 1.06)	• Age
Steinbrecher, 2012*[220]	United States	1998–2002	37,407	Number of cases	Non-specific	Combined	Non-Hispanic Caucasians	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.25	(1.20, 1.30)	• Age
Steinbrecher, 2012*[220]	United States	1998–2002	3,475	Number of cases	Non-specific	Combined	African Americans	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	1.20	(1.03, 1.43)	• Age
Steinbrecher, 2012*[220]	United States	1998–2002	6,427	Number of cases	Non-specific	Combined	Hispanics	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	0.65	(0.59, 0.72)	• Age
Steinbrecher, 2012*[220]	United States	1998–2002	5,299	Number of cases	Non-specific	Combined	Asian/ Pacific Islander	SES quintile: 1st Quintile (low SES)/ 5th Quintile (high SES)	0.96	(0.87, 1.05)	• Age

Author, year	Country of participants recruitment	Reference year	N	Type of N	Target age group	Sex-specific analyses	Race/ ethnicity[#]	Composite indicators (comparison/ reference)	OR	(95% CI)	Adjusted confounders
Doubeni, 2012*[141]	United States	1995–2006	7,676	Number of cases	50–75	Combined	Non-specific	Neighbour deprivation: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.16	(1.05, 1.28)	• Age • Sex • Race and ethnicity • Family history of colorectal cancer • State of residence • Behavioural factors • Education.
Kuznetsov, 2012*[238]	Germany	2003–2006	29,575	Number of cases	Non-specific	Combined	Non-specific	Bavarian index of multiple deprivation quintile: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.25	(1.19, 1.31)	• Age • Sex
Donnelly, 2011[232]	North Ireland	1995–2007	12,671	Number of cases	Non-specific	Combined	Non-specific	The multiple deprivation measure: most deprived decile/ least deprived decile	1.20	(1.14, 1.27)	• Age
Kee, 1996[233]	Ireland	1990–1991	1,144	Number of cases	Non-specific	Combined	Non-specific	Townsend deprivation score quintile: 5th Quintile (most deprived)/ 1st Quintile (least deprived)	1.28	(1.06, 1.53)	• Age • Sex

[#]Race/ethnicity categories as reported in the publication

*were not included in the meta-analyses

Acronyms: N/A=not available

Appendix B table 10 Quality assessment of risk of bias of 34 included studies by using ROBINS-I

Authors, year	**Risk of bias domains**						
	Confounding	**Selection of participants into the study**	**Classification of intervention**	**Deviations from intended interventions**	**Missing data**	**Measurement of outcomes**	**Selection of reported result**
Tweed, 2018[235]	*Serious*	Low	Moderate	Low	Low	Low	Moderate
Canchola, 2017[213]	Moderate	Low	Low	Low	Low	Low	Moderate
Stroup, 2017[221]	Serious	Low	Low	Low	Low	Low	Moderate
Liu 2016[217]	Serious	Low	Low	Low	Low	Low	Moderate
Hastert, 2015[216]	Serious	Low	Low	Low	Low	Low	Moderate
Garcia-Gil, 2014[239]	Serious	Low	Low	Low	Low	Low	Moderate
Miki, 2014[242]	Serious	Low	Moderate	Low	NI	Low	Moderate
Steinbrecher, 2012[220]	Serious	Low	Moderate	Low	Low	Low	Moderate
Leufkens, 2012[240]	Serious	Low	Low	Low	Low	Low	Moderate
Doubeni, 2012[141]	Moderate	Low	Low	Low to moderate	NI	Low	Moderate
Kim, 2012[241]	Serious	Low	Low	Moderate	Low	Low	Moderate
Kuznetsov, 2012[238]	Serious	Low	Moderate	Low	Low	Low	Moderate
Torres-Cintron, 2012[224]	Serious	Low	Moderate	Low	Low	Low	Moderate
Donnelly, 2011[232]	Serious	Low	Moderate	Low	Low	Low	Moderate
Oliphant, 2011[234]	Serious	Low	Moderate	Low	Low	Low	Moderate
Kim, 2010[80]	Serious	Low	Moderate	Low	NI	Low	Moderate
Clegg, 2009[214]	Serious	Low	Low	Low	Low	Low	Moderate
Spadea, 2009[226]	Serious	Low	Moderate	Low	Low	Low	Moderate
de Kok, 2008[230]	Serious	Low	Low	Low	Low	Low	Moderate
Goy, 2008[223]	Serious	Low	Low	Low	Low	Low	Moderate
Egeberg, 2008[236]	Serious	Low	Low	Low	Low	Low	Moderate

Authors, year	Risk of bias domains						
	Confounding	Selection of participants into the study	Classification of intervention	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of reported result
Mouw, 2008[219]	Moderate	Low	Low	Low	Low	Low	Moderate
Braaten, 2005[237]	Serious	Low	Low	Low	Low	Low	Moderate
Pisa, 2000[225]	Serious	Moderate	Low	Low	Low	Low	Moderate
Mackillop, 2000[218]	Serious	Low	Moderate	Low	Low	Low	Moderate
Tavani, 1999[227]	Serious	Moderate	Low	Low	Low	Low	Moderate
Gorey, 1998[222]	Serious	Low	Moderate	Moderate	Low	Low	Moderate
Smith, 1996[243]	Serious	Low	Moderate	Low	Low	Low	Moderate
Kee, 1996[233]	Serious	Low	Low	Low	Low	Low	Moderate
Van Loon, 1995[231]	Moderate	Low	Low	Low	Low	Low	Moderate
Gorey, 1995[215]	Serious	Low	Moderate	Low	NI	Low	Moderate
Faggiano, 1994[228]	Serious	Low	Moderate	Low	NI	Low	Moderate
Vecchia, 1992[229]	Serious	Moderate	Low	Low	Low	Low	Moderate
Baquet, 1991[212]	Serious	Low	Moderate	Low to moderate	Low	Low	Moderate